The Canadian Journal of Neurological Sciences (2023), **50**, 703–709
doi:10.1017/cjn.2022.291

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

Rapid Eye Movement Sleep Behavior Disorder in Parkinson's Disease: A Survey-Based Study

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ABSTRACT: ***Objective:*** To characterize Parkinson's disease (PD) symptoms based on the presence, onset time, and severity of rapid eye movement sleep behavior disorder (RBD) and their association with impulse control disorders (ICD). ***Background:*** RBD is a frequent non-motor symptom in PD, usually described as prodromal. The severity of RBD according to the start time and its relationship with ICD in PD needs further clarification. ***Methods:*** A survey-based study was performed to determine the presence of RBD symptoms, their severity, and the temporal relationship with the PD onset. The survey included RBD1Q, the Mayo Sleep, and the RBDQ-HK questionnaires and questions about clinical characteristics, including ICD. Only PD patients with care partners spending night hours in the same room were included. ***Results:*** 410 PD patients were included: 206 with RBD (50.2%) and 204 non-RBD (49.8%). The PD-RBD patients were younger and their daily levodopa dose was higher than the non-RBD group. Most of these patients developed RBD symptoms after the onset of clinical PD were younger at motor symptom onset and had higher scores in the hallucinations and psychosis subsection of MDS-UPDRS-I. RBD group had a more severe non-motor phenotype, including more ICD than those without RBD, mainly due to higher compulsive eating. ***Conclusions:*** In our study, most patients recognized RBD symptoms after the onset of the PD motor symptoms and the clinical features of PD with and without RBD were distinctive, supporting the hypothesis that PD-RBD might represent a variant pattern of neurodegeneration.

RÉSUMÉ : Troubles du comportement en sommeil paradoxal dans le cas de la maladie de Parkinson : une étude basée sur une enquête. ***Objectif :*** Caractériser les symptômes de la maladie de Parkinson (MP) en fonction de la présence, de l'heure d'apparition et de la gravité des troubles du comportement en sommeil paradoxal (TCSP) et de leur association avec les troubles du contrôle des impulsions (TCI). ***Contexte :*** Les TCSP sont des symptômes non-moteurs fréquents de la MP et sont généralement décrits comme prodromiques. La gravité de ces troubles en fonction de leur heure d'apparition, de même que leur relation avec les TCI dans la MP, doivent être clarifiées davantage. ***Méthodes :*** Une étude basée sur une enquête a été réalisée pour déterminer la présence des symptômes liés aux TCSP, leur gravité ainsi que la relation temporelle avec les débuts de la MP. Cette enquête comprenait les questionnaires RBD1Q, *Mayo Sleep* et RBDQ-HK ainsi que des questions portant sur les caractéristiques cliniques des patients, y compris des TCI. À noter que seuls des patients atteints de la MP dont les proches aidants passent la nuit dans la même pièce ont été inclus dans cette étude. ***Résultats :*** Au total, 410 patients atteints de la MP ont été inclus. De ce nombre, 206 étaient aux prises avec des TCSP (50,2 %) alors que 204 n'en étaient pas atteints (49,8 %). Les patients du premier groupe étaient plus jeunes et leur dose quotidienne de lévodopa était plus élevée que celle des patients du deuxième groupe. La plupart des patients qui ont développé des symptômes de TCSP après l'apparition clinique de la MP étaient plus jeunes au moment de l'apparition des symptômes moteurs; ils avaient aussi des scores plus élevés dans la sous-section «Hallucinations et psychose» du MDS-UPDRS-I. Plus encore, le groupe des patients atteints de TCSP présentait un phénotype non-moteur plus sévère, y compris plus de TCI que les autres patients, et ce, principalement en raison d'une alimentation compulsive plus élevée. ***Conclusions :*** Dans notre étude, la plupart des patients ont fait état de symptômes de TCSP après l'apparition des premiers symptômes moteurs de la MP. Les caractéristiques cliniques de la MP avec et sans symptômes de ce type étaient distinctes, ce qui soutient l'hypothèse selon laquelle la MP combinée à ces symptômes pourrait représenter un modèle varié de neuro-dégénérescence.

Keywords: REM sleep behavior disorder; Parkinson's disease; Severity; Impulse control disorders

(Received 14 April 2022; final revisions submitted 9 August 2022; date of acceptance 10 August 2022; First Published online 26 August 2022)

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Cite this article: Bruno V, Ruiz-Lopez M, Terroba-Chambi C, Freitas ME, Rajalingam R, Chang A, Fox SH, and Lang AE. (2023) Rapid Eye Movement Sleep Behavior Disorder in Parkinson's Disease: A Survey-Based Study. *The Canadian Journal of Neurological Sciences* **50**: 703–709, https://doi.org/10.1017/cjn.2022.291

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Introduction

REM sleep behavior disorder (RBD) is the most recognized type of REM parasomnia. It was first described by Schenck and colleagues in 1986,[1] and it is characterized by repeated episodes of dream-enacting behaviors, sleep-related vocalization, and abnormal motor behaviors linked to REM sleep without atonia (RSWA).[2] RBD prevalence in the general population is approximately 1% in the >50–60-year age group.[3] In Parkinson's disease (PD), the reported prevalence is substantially higher, varying greatly from 20 to 72%.[4] Moreover, RBD is considered the most robust premotor disease marker in PD.[5] Several influential cohort studies have shown that more than 80% of people with "idiopathic" RBD convert to a defined neurodegenerative syndrome, mostly a synucleinopathy (PD, dementia with Lewy bodies and multiple system atrophy), with an overall conversion rate of 6.3% per year if followed for more than 15 years.[6] While some authors have argued that subjects who convert from RBD to PD do not have typical idiopathic PD, pathological evidence suggests that these patients show alpha-synuclein pathology with a likely more significant pathological burden than those who present without the RBD prodrome.[7]

The PD phenotype of RBD subjects who convert to PD or experience PD with concomitant clinical RBD episodes (PD-RBD) is also likely to recapitulate this greater pathological burden with higher rates of cognitive impairment, depression, anxiety, autonomic dysregulation, and other non-motor symptoms in the RBD group compared to those without RBD.[8] The most prominent and common symptoms associated with RBD conversion to PD are olfactory dysfunction and constipation, while sleep disorders and depression may appear before the onset of motor symptoms, and the cognitive impairment often appears last.[9]

On the other hand, the association between RBD and impulse control disorders (ICD) in PD is not fully understood. Previously published results are controversial and sometimes inconclusive, triggering controversies about the association of ICD and PD-RBD. While some authors showed a clear association,[8,10-12] others failed to find one.[4,13-15] For instance, a large controlled series of patients with PD and ICD assessed with video polysomnography by Fantini et al. found that participants with ICD had a higher arousal index and higher RSWA than those without RBD (51.9% ± 28.2% vs. 32.2 ± 27.1%, $p = 0.004$).[10] Additionally, RBD was more frequent in the ICD group (85% vs. 53%, $p = 0.0001$). On the contrary, a large longitudinal study by Baig et al. looking particularly at this potential association found that prevalence in the RBD group (1%) was similar to that in controls (0.7%).[13] Differences between studies may be ascribed to methodological differences in assessing RBD and ICD, insufficient power due to a low number of patients with ICD, and incomplete age-sex-severity-matching between groups.

Despite the wealth of awareness about the relationship between RBD and PD, the natural evolution of this disorder in PD is poorly understood. A recent publication reported that those participants with PD and RBD followed longitudinally had more severe baseline motor and non-motor symptoms, including a faster motor progression and more cognitive impairment.[16] Still, literature on phenotypes regarding start time and severity of the RBD symptoms is incomplete.

This study aimed to examine and clarify two crucial aspects of RBD in PD because both are essential for future neuroprotective trials and clinical care. First, elucidating whether PD-RBD constitutes a distinct phenotype with a unique etiology and disease course or is indistinguishable from idiopathic PD without RBD, and, secondly, to add clarification to the association between PD, RBD, and ICD.

Methods

Study Design and Participants

This was a survey-based study performed in an individual in-person interview with participants with the clinical diagnosis of PD. Data were collected from PD patients approached during routine outpatient visits at the movement disorder center at the Toronto Western Hospital between January 2015 and December 2017. This study was approved by the Ethics Committee of the University of Toronto, and written informed consent was obtained from all participants.

Study Assessments

The study was divided into two phases.

First Phase

All PD patients with or who never had RBD (non-RBD) were included. Demographic data (age, gender, age at onset of PD, current medication, and previous treatments) were collected, as well as non-motor symptoms (MDS-UPDRS part I), motor symptoms (MDS-UPDRS part III), and motor complications (MDS-UPDRS part IV) at the time of the interview. The Questionnaire for Impulsive-Compulsive Disorders in PD[17] was used to address the history of ICD. Sleep-related complaints and habits were investigated using questionnaires. Initial screening for the presence of RBD was done using the validated single-question screening tool for RBD (RBD-Q1)[18] and the Mayo Sleep Questionnaire,[19] both of them had to be answered by patients and bed partners/care partners. Only those PD who reported RBD symptoms at any point in their lives, and these symptoms were confirmed by the bed partners (or care partners who spent night hours in the same room), continued with the second phase of the study and were asked to complete the RBD questionnaires. Information regarding the response of RBD symptoms to antiparkinsonian medication and advanced therapies for PD (deep brain stimulation and intestinal levodopa infusion therapy) and a short questionnaire regarding specific treatments for RBD were also compiled. Levodopa dose equivalents were calculated based on the scheme of Tomlinson and coworkers.[20]

Second Phase

PD patients and bed partners/care partners were asked to retrospectively provide information about their RBD symptoms onset, intensity, and the relationship between them and the onset of PD using the RBD questionnaire-Hong Kong (RBDQ-HK).[21] The RBDQ-HK is a self-administered questionnaire that can be filled in also by or in collaboration with the bed partner. It comprises 13 questions assessing different clinical features of RBD. In addition, the RBDQ-HK questionnaire was used to evaluate the evolution of RBD symptoms over time to compare the severity of RBD symptoms at two different time points: the first year after symptom onset and, most recently, in the last year. Responses were scored on a five-point scale (none = 0, yes/once or a few times a year = 1, once or a few times a month = 2, 1-2 times a week = 3, 3 or more times a week = 4). The RBD total score was calculated by adding the frequency items.

https://doi.org/10.1017/cjn.2022.291 Published online by Cambridge University Press

Statistical Analysis

Data were tested for normal distribution, and results were presented as mean ± SD. Differences in demographic and clinical features between groups were evaluated using an unpaired *t*-test for quantitative variables. Categorical data were compared employing a Wilcoxon signed-rank test. All *p* values were two-tailed, and significance was set at $p < 0.05$. Multiple variables logistic regression models were used to exclude the presence of confounders or effect modifiers when applicable. Variables were checked for collinearity. All analyses were performed using Stata v16.0.

Results

Demographic and Clinical Characteristics

Four hundred and ten PD patients were included in the first phase, of which 206 (50.2%) reported RBD and 204 (49.8%) non-RBD. Ninety PD-RBD patients (21.6% of the total and 43.7% of the PD-RBD patients) completed all the questionnaires. All of the 90 PD-RBD patients were included in the second phase. In both groups (PD-RBD and PD-non-RBD) males predominated but more so in PD-RBD (73.3% vs. 63.7%, $p = 0.037$). PD- RBD patients were younger at disease onset (55.0 ± 9.6 vs. 57.0 ± 10.7, $p = 0.045$), and their levodopa daily dose was higher (869.4 ± 428.9 mg vs. 776.2 ± 479.9 mg, $p = 0.039$) than the non-RBD group. Comparing non-motor aspects of daily living experiences, the RBD group showed worse scores in cognition, psychosis, depression, anxiety, apathy, daytime sleepiness, urinary problems, constipation, lightheadedness, and fatigue subsections, respectively (see Table 1). Multiple variable logistic regression models adjusting for gender, disease duration, current age, and age at PD onset confirmed that in the presence of RBD higher odds of reporting hallucinations and psychosis (odds ratio (OR) 2.50, 95% confidence interval (CI) 1.56-4.01, *p* value < 0.001) and constipation (OR 1.46, 95% CI 1.17-1.84, *p* value 0.001) when compared to patients without RBD. No other differences were found in other clinical characteristics such as MDS-UPDRS-III (motor) and IV (motor complications) (see Table 1). No relationship was found between any of the antiparkinsonian medications and RBD symptoms.

Association Between ICD and RBD

ICD were more frequent in the RBD group (31.1 vs. 20.6%, $p = 0.016$) mainly due to higher compulsive eating (13.6 vs. 3.9%, $p = 0.001$) and hypersexuality (8.7 vs. 3.9%, $p = 0.045$). Compulsive eating showed significant differences between groups, regardless of their treatment with dopamine agonists (DAs) (21.1 vs. 5.8%, $p = 0.001$). In hypersexuality, a tendency to significance was observed between groups treated and not with DA (13 vs. 5.8%, $p = 0.054$) (see Table 1). Multiple variable logistic regression models adjusting for gender, disease duration, current age, and age at PD onset confirmed that in the presence of RBD the OR of reporting compulsive eating was 5.13 (95% CI 1.71-15.11, *p* value 0.003) when compared to patients without RBD. The association between RBD and hypersexuality was not maintained when adjusting for multiple variables (OR 1.46, 95% CI 0.55-3.85, *p* value 0.44).

Start Time and Severity of RBD Symptoms

In the 90 PD who completed all the questionnaires, 64 (71.1%) developed RBD symptoms after the onset of PD, and 26 (28.9%) reported clear prodromal RBD. PD patients who developed RBD after the onset of motor PD were younger at disease onset (53.1 ± 9.4 vs. 57.7 ± 7.4 years, $p = 0.027$). In addition, they had higher scores in the hallucinations and psychosis subsection of MDS-UPDRS (0.1 ± 0.3 vs. 0.5 ± 0.9, $p = 0.014$) than those who reported prodromal RBD. No other differences were found between groups (see Table 2). There were no differences between groups regarding the trajectory of RBD symptoms in terms of severity during the first year, over the past year, or the state of the RBD symptoms at the time of the survey. Five patients reported remission of the RBD symptoms, one of them with prodromal RBD noted remission of RBD symptoms after the onset of the PD motor symptoms, and four in the group whose RBD symptoms began after the onset of motor PD (see Table 2).

Discussion

In this retrospective survey-based study, we investigated the association of motor, and non-motor symptoms of PD, with a priority focus on ICD, and self-reported RBD features in order to characterize phenotypes based on the onset time and severity of RBD symptoms related to PD motor onset. Employing data from one of the largest PD studies, in which movement disorder specialists interviewed PD and their care partners, our results support many findings previously proposed in the literature. In addition, we confirmed that RBD features are a clinical marker for higher non-motor disability while providing new insights into ICD and PD-RBD association.

It has been reported that 30–80% of PD have RBD symptoms.[22,23] In our sample, 50.2% of PD reported RBD. Male predominance was observed in both groups (PD-RBD and PD-non-RBD), but the frequency of males was significantly higher in the PD-RBD group. PD-RBD group also differed from those without RBD showing a worse non-motor symptom profile impacting daily living activities, with an early PD onset, higher prevalence of ICD, and higher requirement of levodopa treatment. In line with our results, previous studies have shown that PD-RBD exhibits clinical heterogeneity for motor and non-motor symptoms compared with PD without RBD.[24-27] Clinical, neuropsychological, and imaging studies consistently show that RBD in PD represents a marker of an aggressive phenotype, paralleled with a more widespread degenerative process.[24,28] It has been suggested that the PD-RBD phenotype may show features such as autonomic dysfunction, hallucinations, more axial symptoms, and faster cognitive decline.[24,26] PD-RBD group tend to have the akinetic/rigid-dominant subtype of PD[27] and exhibit severe non-motor symptoms[26,27,29] and higher levodopa needs.[25] Moreover, a meta-analysis by Zhu et al.[28] aiming to evaluate the clinical variations in PD with or without Confirmed or Probable-RBD (based on polysomnogram confirmation) was able to show that regardless of the RBD evaluation method, some factors are constant in the PD-RBD association, for instance, increased Hoehn-Yahr scale, higher UPDRS-III score, and longer disease duration. In addition, confirmed-RBD was more frequent in males and elderly PD.[28]

Onset Time and Severity of RBD in PD

It is well recognized that RBD may precede the development of PD motor syndromes by 3–13 years[22] with a mean duration of 10–12 years between RBD diagnosis and PD motor syndromes.[23,30] It may precede motor symptoms or develop after PD onset; indeed, clinical manifestations of PD could vary depending on the timing of RBD onset.[9] We identified critical differences between PD patients reporting RBD symptoms before or after the onset of

https://doi.org/10.1017/cjn.2022.291 Published online by Cambridge University Press

Table 1: Demographic characteristics of patients with (PD-RBD) and without RBD (PD-non-RBD)

	PD-RBD $n = 206$	PD-non-RBD $n = 204$	p value
Sex M/F, *n* (%)	151/55 (73.30/26.70)	130/74 (63.73/36.27)	**0.037***
Current age (years), mean (SD)	66.90 (8.63)	66.84 (10.01)	0.948
AAO (years), mean (SD)	55.00 (9.58)	57.01 (10.68)	**0.045**
LD dose (mg), mean (SD)	869.45 (428.90)	776.18 (479.93)	**0.039**
DA, *n* (%)	123 (59.71)	121 (59.31)	0.935
ICD, *n* (%) [Treated with DA (%)]	64 (31.07) [56 (45.53)]	42 (20.59) [41 (33.88)]	**0.015** 0.063
Punding, *n* (%) [Treated with DA (%)]	4 (1.94) [2 (1.63)]	2 (0.98) [1 (0.83)]	0.418 0.571
Compulsive eating, *n* (%) [Treated with DA, *n* (%)]	28 (13.59) [26 (21.14)]	8 (3.92) [7 (5.79)]	**0.001*** **0.001***
Hypersexuality, *n* (%) [Treated with DA, *n* (%)]	18 (8.74) [16 (13.01)]	8 (3.92) [7 (5.79)]	**0.045** 0.054
Gambling, *n* (%) [Treated with DA, *n* (%)]	13 (6.31) [12 (9.76)]	18 (8.82) [17 (14.05)]	0.336 0.301
Excessive shopping, *n* (%) [Treated with DA (%)]	12 (5.83) [11 (8.94)]	9 (4.41) [8 (6.61)]	0.517 0.497
Excessive hobbies, *n* (%) [Treated with DA (%)]	7 (3.40) [6 (4.8)]	9 (4.41) [9 (7.4)]	0.596 0.406
DDS, *n* (%) [Treated with DA (%)]	4 (1.94) [2 (1.63)]	4 (1.96) [3 (2.48)]	0.988 0.638
MDS-UPDRS			
Part 1. Non-Motor Aspects of Experiences of Daily living			
I.1 Cognitive impairment, mean (SD)	1.31 (1.16)	0.80 (1.06)	**<0.001**
I.2 Hallucinations and psychosis, mean (SD)	0.50 (0.93)	0.10 (0.40)	**<0.001***
I.3 Depressed mood, mean (SD)	0.97 (0.99)	0.67 (0.89)	**0.002**
I.4 Anxious mood, mean (SD)	1.10 (1.04)	0.90 (0.94)	**0.042**
I.5 Apathy, mean (SD)	0.86 (0.98)	0.61 (0.87)	**0.007**
I.6 Features of dopamine dysregulation syndrome, mean (SD)	0.28 (0.80)	0.27 (0.71)	0.911
I.7 Sleep problems, mean (SD)	1.71 (1.07)	1.41 (1.22)	**0.008***
I.8 Daytime sleepiness, mean (SD)	1.50 (0.95)	1.23 (0.91)	**0.003**
I.9 Pain and other sensations, mean (SD)	1.25 (1.23)	1.27 (1.21)	0.895
I.10 Urinary problems, mean (SD)	1.33 (1.14)	1.03 (1.01)	**0.005**
I.11 Constipation problems, mean (SD)	1.34 (1.05)	0.89 (1.03)	**<0.001***
I.12 Lightheadedness on standing, mean (SD)	0.81 (1.01)	0.58 (0.90)	**0.015**
I.13 Fatigue, mean (SD)	1.49 (1.07)	1.40 (1.83)	0.54
Part III. Motor Examination (ON), mean (SD)	22.50 (11.10)	20.47 (10.47)	0.057
Part IV mean. Motor complications, mean (SD)	2.87 (2.65)	2.58 (2.73)	0.283

RBD=REM sleep behavior disorder; AAO=age at onset; LD=levodopa; DA=dopaminergic agonist; ICD=impulse control disorders; DDS=dopamine dysregulation syndrome; MDS-UPDRS=Movement Disorder Society version of Unified Parkinson´s disease Rating Scale; Part I= non-motor aspects of daily living: I.1: cognition impairment; I.2: hallucinations and psychosis; I.3: depression; I.4: anxiety; I.5: apathy; I.6: dopamine dysregulation syndrome; I.7: sleep; I.8: daytime sleepiness; I.9: pain; I.10: urinary problems; I.11: constipation; I.12: lightheadedness; I.13: fatigue; Part III=motor symptoms; Part IV: motor complications.
Significant values at $p < 0.05$ comparisons unpaired *t*-test or Wilcoxon signed-rank test are presented in bold.
*The differences between groups were maintained after multiple variable regression models adjusting for gender, disease duration, current age, and age at PD onset. SD indicates standard deviation.

PD motor symptoms. Those patients who reported RBD symptoms after the onset of PD motor manifestations had an onset of the disease up to 4 years earlier with more psychotic symptoms than the group with prodromal RBD. This preliminary finding requires further exploration but suggests that the onset of RBD after motor symptoms is associated with a more aggressive clinical presentation in the PD-RBD phenotype.

In line with our results, other authors reported interesting clinical differences associated with the timing of RBD onset. For instance, Ferri et al.[25] found in their population that patients in

https://doi.org/10.1017/cjn.2022.291 Published online by Cambridge University Press

Table 2: Comparisons between patients who developed RBD before and after motor symptoms of PD

	RBD Before PD $n = 26$	RBD After PD $n = 64$	p value
Males, *n* (%)	20 (76.92)	48 (75)	0.848
Age (years), *n* (%)	66.15 (6.55)	66.18 (7.97)	0.985
AAO, *n* (%)	57.73 (7.39)	53.10 (9.37)	**0.027***
ICD, *n* (%)	6 (23.08)	22 (34.38)	0.297
Punding, *n* (%)	0	1 (1.56)	0.524
Compulsive eating, *n* (%)	2 (7.69)	9 (14.06)	0.406
Hypersexuality, *n* (%)	2 (7.69)	8 (12.50)	0.513
Gambling, *n* (%)	1 (3.85)	3 (4.69)	0.861
Excessive shopping, *n* (%)	1 (3.85)	4 (6.25)	0.654
Excessive hobbysm, *n* (%)	1 (3.85)	4 (6.25)	0.654
DDS, *n* (%)	0	3 (4.69)	0.264
DBS users, *n* (%)	4 (16.67)	22 (34.38)	0.277
Start time and severity of RBD**			
Maximum severity of RBD, mean (SD)	20.5 (9.39)	20.17 (11.26)	0.896
Severity in first year, mean (SD)	9.57 (8.19)	10.96 (10.16)	0.537
Severity in last year, mean (SD)	15.23 (7.99)	16.01 (10.50)	0.733
Current RBD, *n* (%) (trajectory)	25 (96.15)	60 (93.75)	0.654
RBD remission, *n* (%)	1 (3.85%)	4 (6.25)	0.646
RBD remission after PD, *n* (%)	1 (3.85)	3 (4.69)	0.646
MDS-UPDRS			
Part 1. Non-Motor Aspects of Experiences of Daily living			
I.1 Cognitive impairment, mean (SD)	1.03 (0.99)	1.5 (1.14)	0.075
I.2 Hallucinations and psychosis, mean (SD)	0.07 (0.27)	0.54 (0.94)	**0.014***
I.3 Depressed mood, mean (SD)	0.84 (0.88)	0.82 (0.84)	0.928
I.4 Anxious mood, mean (SD)	0.88 (0.99)	0.92 (1.01)	0.874
I.5 Apathy, mean (SD)	0.76 (0.99)	0.71 (0.86)	0.810
I.6 Features of dopamine dysregulation syndrome, mean (SD)	0.03 (0.19)	0.125 (0.57)	0.458
I.7 Sleep problems, mean (SD)	1.84 (1.12)	1.56 (1.02)	0.249
I.8 Daytime sleepiness, mean (SD)	1.19 (0.74)	1.34 (1.02)	0.498
I.9 Pain and other sensations, mean (SD)	0.96 (0.87)	1.04 (1.21)	0.746
I.10 Urinary problems, mean (SD)	0.96 (0.91)	1.34 (1.21)	0.151
I.11 Constipation problems, mean (SD)	1.30 (0.92)	1.28 (1.01)	0.909
I.12 Lightheadedness on standing, mean (SD)	0.42 (0.80)	0.67 (1.03)	0.278
I.13 Fatigue, mean (SD)	1.46 (1.02)	1.39 (1.01)	0.76
Part III. Motor examination (ON), mean (SD)	20.38 (10.65)	22.68 (10.19)	0.334
Part IV. Motor complications, mean (SD)	2.30 (2.39)	3.01 (2.59)	0.234

NA=not applicable; RBD=REM sleep behavior disorder; AAO=age at onset; ICD=impulse control disorders; DDS=dopamine dysregulation syndrome; DBS=deep brain stimulation; MDS-UPDRS=Movement Disorder Society version of Unified Parkinson´s disease rating scale; Part I=non-motor aspects of daily living: I.1: cognition impairment; I.2: hallucinations and psychosis; I.3: depression; I.4: anxiety; I.5: apathy; I.6: dopamine dysregulation syndrome; I.7: sleep; I.8: daytime sleepiness; I.9: pain; I.10: urinary problems; I.11: constipation; I.12: lightheadedness; I.13: fatigue; Part III: motor symptoms; Part IV= motor complications.

*Significant at $p < 0.05$ comparisons unpaired *t*-test or Wilcoxon signed-rank test are presented in bold. SD indicates standard deviation. **The maximum severity of RBD was assessed using the RBDQ-HK. The frequency at which patients or their bed partners/care partners reported episodes of RBD scored on a 5-point scale where 0 = none and 4 = 3 or more times per week.

whom RBD developed concomitantly or after the onset of PD motor symptoms had more severe symptoms, received higher doses of dopaminergic therapy, and had a longer disease duration than patients with prodromal RBD or those with PD without RBD who did not differ in those disease parameters.

Similarly, Gong et al.[31] found that worse cognition was associated with a shorter interval of RBD preceding PD onset, but not RBD duration. Nomura et al.[32] found more significant cognitive impairment in patients with RBD starting after PD onset than in those with prodromal RBD despite similar motor and

https://doi.org/10.1017/cjn.2022.291 Published online by Cambridge University Press

autonomic dysfunction with similar dopaminergic agents. Our findings support these authors' hypothesis that PD with prodromal RBD and PD with RBD symptoms after motor onset might constitute two possibly distinct clinical and pathophysiological groups, likely based on different progressive neuropathological sequences of events. This might also comply with the "brain first / body first" subdivision proposed by Horsager et al.[33] in which de novo patients lacking RBD by the first year of clinical PD have more evidence of a top-down progression of features.

Relationship Between ICD and PD-RBD

ICD are behavioral addictions that may be debilitating for the patient or others. They negatively impact the quality of life of patients and their care partners,[34] remain underdiagnosed, lack clear recommendations regarding therapy, and may lead to severe social and legal consequences.[35]

The estimated prevalence of ICD in PD is about 14%, while up to 31% experience at least one ICD during their illness.[34] In a recent longitudinal study of severity of ICD in PD-RBD, Baig et al.[13] reported a prevalence of 19% in early PD. In our study, the prevalence of ICD in the PD-RBD group was 31% and significantly higher than in the group without RBD (21%), mainly related to hypersexuality and compulsive eating. The high variability in the reported prevalence of ICD in PD-RBD could be explained by the heterogeneity of the PD phenotype and due to the absence of semi-structured baseline interviews conforming to DSM-5 diagnostic criteria (or aligned with DSM-5).[13]

PD-RBD has been reported to have a twofold higher risk of developing ICD,[10,36] suggesting that a specific pattern of neurodegeneration may predispose to the emergence of ICD in the context of dopaminergic medications.[12] Notwithstanding, no longitudinal studies are currently available to estimate the actual risk of developing ICD over time in PD with and without RBD taking dopaminergic replacement therapy. However, taken together, cross-sectional data suggest that PD-RBD may have an increased vulnerability to developing ICD, compared to PD-non-RBD, probably due to more severe impairment in the meso-corticolimbic pathway.[29]

Although the mechanisms underlying ICD are not yet fully understood, the primary driver is thought to be dopaminergic medication, particularly DAs.[13] Our study supports the coexistence of DA treatment and ICD in those PD patients who reported hypersexuality (see Table 1). Furthermore, recent findings[12] on the volumetric and functional connectivity characteristics of the reward system of patients with idiopathic RBD concluded that PD-RBD might ultimately predispose these individuals to the onset of ICD when receiving dopaminergic medications, following the onset of motor symptoms. These findings are supported by the fact that altered functional connectivity between limbic, striatal, and posterior cortical regions was associated with hypersexuality.[12] Further studies are needed to confirm the nature of this relationship and its pathophysiology.

Strengths and Limitations

While the retrospective design of our study allowed for a large and diverse patient group, it is also a limitation given potential recall bias of REM behavior events and clinical information, including the possibility of participants reporting non-REM parasomnias, as well as lack of information about potentially relevant variables such as education level and smoking habit. In addition, although screening questionnaires or a history of abnormal sleep behaviors (mainly when obtained from the bed partner) can be highly suggestive of RBD in the appropriate context, formal diagnosis according to International Classification of Sleep Disorders (2014) requires a polysomnogram, as demonstrated by studies describing any relationship between the beginning of RBD symptoms and PD onset.[25,31,32] Thus, we recommend considering the groups reporting RBD in this study as "probable-RBD" since it was based on clinical validated scales but not polysomnography confirmed. We attempted to improve the accuracy of the diagnosis by only including those RBD cases with confirmation from the bed partners/care partners. Our study in a large sample supports the findings of the previous smaller studies[9,25,28,31,32] that used polysomnogram confirmation reinforcing the value of survey screening methods in assessing RBD. We did not find a significant benefit of dopaminergic therapy on PD-RBD. However, our results are probably affected by the study design and should be interpreted with caution. We could not conduct more extensive analyses of medication data due to the low percentage of PD who were able to provide reliable answers to the questions about the impact of PD medications in the second study phase. On the other hand, the use of some medications can also trigger RBD or RSWA episodes, as a recent literature review showed the most robust evidence for clomipramine, selegiline, and phenelzine,[37] and other antidepressants. We cannot exclude the possibility that some differences observed between the groups with prodromal RBD and those developing RBD after PD onset were related to the undocumented intake of antidepressants known as worsening RBD symptoms since this variable was not compared between groups.

In summary, ours is the most extensive survey-based study to describe PD characteristics based on the timing of RBD onset with respect to the clinical motor symptoms. Our results suggest that patients in the PD-RBD group are younger, use higher doses of levodopa, and have a more severe non-motor phenotype, including more ICD than those without RBD. In this study, most PD patients reported that RBD symptoms began after the onset of motor manifestations. These clinical features of PD with and without RBD support the hypothesis that PD-RBD may represent an alternative pattern of neurodegeneration. However, our study design requires a cautious interpretation of the identified variables associated with RBD-PD. Further investigations are needed to define the distinct features of PD-RBD and explore the still uncertain link between ICD-RBD in PD.

Acknowledgments. The authors thank the participants for taking part in this study.

Conflict of Interest. None of the authors have any conflicts of interest to report.

Statement of Authorship. 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical analysis: A. Design, B. Execution, C. Review and critique; 3. Manuscript preparation: A. Writing of the first draft, B. Review and C. Critique.

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https://doi.org/10.1017/cjn.2022.291 Published online by Cambridge University Press

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https://doi.org/10.1017/cjn.2022.291 Published online by Cambridge University Press