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REM sleep behaviour disorder in Parkinson's disease is associated with specific motor features

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See Editorial Commentary, p 1087

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ABSTRACT

Background: Rapid eye movement (REM) sleep behaviour disorder (RBD) is commonly associated with Parkinson's disease (PD), and recent studies have suggested that RBD in PD is associated with increased cognitive impairment, waking EEG slowing, autonomic impairment and lower quality of life on mental health components. However, it is unclear whether the association of RBD in PD has implications for motor manifestations of the disease.

Methods: The study evaluated 36 patients with PD for the presence of RBD by polysomnography. Patients underwent an extensive evaluation on and off medication by a movement disorders specialist blinded to the polysomnography results. Measures of disease severity, quantitative motor indices, motor subtypes, complications of therapy and response to therapy were assessed and compared using regression analysis that adjusted for disease duration and age.

Results: Patients with PD and RBD were less likely to be tremor predominant (14% vs 53%; $p<0.02$) and had a lower proportion of their Unified Parkinson Disease Rating Scale (UPDRS) score accounted for by tremor (8.2% vs 19.0%; $p<0.01$). An increased frequency of falls was noted among patients with RBD (38% vs 7%; $p = 0.04$). Patients with RBD demonstrated a lower amplitude response to their medication (UPDRS improvement 16.2% vs 34.8%; $p = 0.049$). Markers of overall disease severity, quantitative motor testing and motor complications did not differ between groups.

Conclusions: The presence of altered motor subtypes in PD with RBD suggests that patients with PD and RBD may have a different underlying pattern of neurodegeneration than PD patients without RBD.

Although Parkinson's disease (PD) is often conceived of as a relatively uniform process, severity of disease and clinical manifestations can differ radically between individuals. For example, in a recent 10-year prospective study, 13 of 126 patients with PD had experienced no functional disability whereas at the other extreme, nine patients were wheelchair users or bed bound.[1] At present, our understanding of the pathophysiological basis of these profound differences in clinical manifestations is limited. In prospective studies, the only factors that have been consistently associated with poor prognosis are baseline disease severity, absence of rest tremor and older age of onset.[2]

Rapid eye movement (REM) sleep behaviour disorder (RBD) is characterised by loss of the normal muscle atonia that accompanies REM sleep.[3 4] Affected patients have excessive motor activity in association with dream content. Although few autopsy studies have been performed, it has been suggested that degeneration of nuclei in the pontine tegmentum and medial medulla are responsible for the loss of atonia during sleep.[5 6] RBD is commonly associated with PD—polysomnographic studies at our centre have estimated that 58% of patients have some loss of REM atonia during sleep.[7] Motor manifestations of PD are classically associated with degeneration of the substantia nigra pars compacta (SNpc), although degeneration also occurs in many brainstem and cortical structures.[8] If RBD is a disease of pontine structures, one could speculate that RBD in PD may be a marker of a degenerative process that has a different (perhaps more widespread) distribution than that found in PD without RBD. If this is the case, the presence of RBD in PD may be associated with differences in motor manifestations. Studies in our centre have previously found that patients with PD and RBD are more likely to have cognitive impairment and slowing of the waking EEG than patients without RBD.[9 10] We also have found that patients with PD and RBD have more autonomic dysfunction than those without.[11] In this study, we conducted an extensive assessment of motor manifestations in patients with PD to determine if RBD was associated with differences in the nature and severity of manifestations.

METHODS

Patient selection

Evaluations were carried out at the sleep disorders laboratory at the Hôpital du Sacré Coeur, Montreal, Quebec, and ethics approval was obtained from the research ethics board of the hospital. All patients gave informed consent to participate in the study according to the declaration of Helsinki.

A consecutive sample of patients with PD from the McGill University Health Centre were assessed for participation (an additional seven patients were recruited from the patient list of a previous study[7]). Patients were eligible for inclusion if they had parkinsonism, as defined by the UK Parkinson Disease Society Brain Bank criteria,[12] and if idiopathic PD was the likeliest cause. To allow as broad a spectrum of disease as possible, patients were excluded only if they had dementia (defined as a Mini-Mental State Examination score of <24 with functional impairment as a result of cognitive loss) or if, after comprehensive assessment, an alternate cause of parkinsonism was thought to be more likely than idiopathic PD.

Polysomnographic evaluation and definition of RBD

All participants were studied in the sleep laboratory for one night, and a sleep specialist (JM) reviewed all clinical sleep evaluations. REM sleep

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was scored according to a method developed for RBD which uses EEG and electro-oculograms only.[13] Recordings of oral and nasal airflow, thoracic and abdominal movements, and oximetry were performed to rule out sleep apnoea. The diagnosis of RBD was made according to the international classification of sleep disorders II criteria as the presence of REM sleep without atonia and of at least one of the following: (1) history of harmful or potentially harmful motor manifestations that could disrupt sleep continuity; or (2) presence of complex motor behaviours during REM sleep seen on the polysomnographic synchronised videotape recording.[14]

Patient evaluation

One movement disorders specialist (RP) performed a comprehensive evaluation of each patient's disease. This evaluation was performed blinded to the results of the polysomnographic evaluation (blinding was not possible for three patients because of participation in a previous study[15]). Evaluations were done in both the medication "off" and "on" state. The "off" state evaluation was performed in the morning, at least 12 h after the previous dose of medication. The "on" state evaluation was performed 1.5 h after taking the usual dose of morning medications.

Measures of interest included:

1. Severity of disease and motor disability. All patients underwent a systematic history and a complete neurological examination that included all components of the Unified Parkinson Disease Rating Scale (UPDRS).[16] Results of overall disease severity have been reported elsewhere.[11] Scores on UPDRS parts II and III were assessed in both the "on" and "off" states; to assess short duration response to medication, the change in UPDRS scores between the on and off state was calculated.
2. Quantitative motor testing. Three quantitative motor indices were used. The first was the Alternate Tap Test, a test of motor speed in the hands with a moderate requirement of coordination and accuracy.[17] Subjects used their index finger to tap two alternating 2.5 cm diameter metal discs attached to a manual counter, mounted 20 cm apart. Two trials in each hand were performed with 1 min provided for each trial, and the average number of taps in both hands was the outcome measure. The second index was the Purdue Peg Board, a test of hand dexterity, motor speed and coordination.[18] Subjects were given 30 s to transfer pins one at a time from a dish into corresponding holes. This was performed separately in each hand, and the average number of pins placed was the outcome measure. The third index was a "timed up and go" test, a measure of gait and transfer speed.[19] Subjects were instructed to rise quickly from a chair, walk 3 m, turn and return to sit in the same chair. The average time required in the two trials was the outcome measure. Each measure was performed in both the medication "on" and "off" states.
3. Motor subtypes. Patients were divided into tremor dominant, akinetic rigid and mixed subtypes, using UPDRS based criteria developed by Schiess *et al*.[20] In addition, the proportion of UPDRS part III "off" motor scores accounted for by each cardinal motor feature was assessed. For tremor, the total score for questions 20 and 21 (seven items) was divided by the total UPDRS part III score. Similar calculations were made to assess the proportion accounted for by rigidity (question 22, five items), bradykinesia (questions 23–26 and 31, nine items), gait/postural stability (questions 27–30, four items) and bulbar abnormalities (questions 18 and 19, two items). The initial cardinal motor manifestation of PD (ie, tremor, bradykinesia or gait dysfunction) was defined by patient self-report. UPDRS examination scores were also subdivided into axial and limb divisions, in a manner similar to that published previously.[21] Axial signs were defined as scores on questions 18, 19, 22 and 27–30, and limb signs were defined as scores on questions 20–26. The ratio between the summed axial and limb scores was then calculated. Finally, the frequency of falls (excluding falls from bed as a result of RBD), freezing, choking and drooling were determined by summing the number of patients who scored $\geqslant 1$ on questions 14, 13, 7 and 6 on either the "on" or "off" components of the UPDRS part II.
4. Motor complications of therapy. Based on history and examination, patients were classified according to whether they had experienced fluctuations or dyskinesia. In addition, motor fluctuation scores (UPDRS questions 36–39) and dyskinesia scores (questions 32–34) were summed to assess the severity of motor complications of dopaminergic therapy.

Table 1 Demographic and basic disease characteristics

	RBD (n = 21)	No RBD (n = 15)	p Value
Sex (men:women)	17:4	8:7	0.14
Age (years)	68.0 (8.6)	65.5 (9.3)	0.41
Levodopa dose (mg equivalents)	430.5 (310.3)	424.7 (312.2)	0.96
Use of dopamine agonist (yes:no)	8:13 (38%)	7:8 (47%)	0.74
Use of other PD medication (yes:no)	6:15 (28%)	7:8 (47%)	0.31
Disease duration (y) (range)	5.7 (3.3) (1–12)	7.3 (4.8) (2–16)	0.24
Hoehn and Yahr score	2.4 (0.9)	2.5 (0.7)	0.83
UPDRS part II-on	12.1 (5.6)	10.9 (6.1)	0.65
UPDRS part II-off	13.2 (6.4)	13.5 (5.5)	0.28
UPDRS part III-on	23.0 (9.3)	20.9 (11.9)	0.54
UPDRS part III-off	27.0 (11.2)	31.3 (9.4)	0.28

Data for continuous variables are presented as mean (SD).
PD, Parkinson's disease; RBD, REM sleep behaviour disorder; UPDRS, Unified Parkinson Disease Rating Scale.

Statistical analysis

Analysis of descriptive variables was done using two tailed t tests and χ^2 tests where appropriate. Multiple logistic regression and multiple linear regression analyses were used to determine the independent relation between the PD measures of interest and RBD, controlling for age and duration of disease. Each PD measure served as a dependent variable, with RBD as the independent variable. For dichotomous measures in which regression could not be reliably performed (because of "0" values), Fisher's exact test was used. Alpha was set at 0.05.

RESULTS

Patient recruitment

A total of 65 patients were approached for participation in the study, and 36 completed the study. Nineteen patients (seven women), four with a clinical history of RBD and 15 without, declined to participate. Eight patients (five women), four with a clinical history of RBD and four without, were excluded because of dementia. An additional two patients were excluded after polysomnography because an alternate cause of parkinsonism was felt to be present: the first (with RBD) had extremely severe autonomic dysfunction and poor response to levodopa and was diagnosed as probable multiple system atrophy; and the second (without RBD) demonstrated only resting tremor without rigidity and bradykinesia after 15 years of disease and did not

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Table 2 Motor subtypes

	RBD (n = 21)	No RBD (n = 15)	Regression RBD main effect (SE)	p Value
Tremor (% of UPDRS III)	8.2 (9.2)	19.0 (15.2)	−0.11 (0.04)	0.01
Initial symptom = tremor (yes:no)	5:16 (24%)	9:6 (60%)	−1.93 (0.91)	0.034
Scheiss classification[20] (akinetic rigid:tremor+mixed)	18:3 (86%)	7:8 (47%)	2.37 (0.99)	0.017
Rigidity (% of UPDRS III)	21.4 (8.6)	18.1 (9.8)	0.025 (0.03)	0.42
Bradykinesia (% of UPDRS III)	46.5 (11.0)	44.0 (19.3)	0.03 (0.053)	0.56
Gait (% of UPDRS III)	11.5 (6.8)	9.7 (5.9)	0.02 (0.02)	0.40
Freezing (yes:no)	8/13 (38%)	2/13 (13%)	1.91 (1.13)	0.091
Falls (yes:no)	8/13 (38%)	1/14 (7%)	2.62 (1.29)	0.044
Bulbar (% of UPDRS III)	12.4 (5.7)	9.2 (4.7)	0.033 (0.019)	0.093
Choking (yes:no)	6/15 (29%)	3/12 (20%)	0.88 (0.91)	0.331
Drooling (yes:no)	11/10 (52%)	10/5 (67%)	−0.54 (0.73)	0.465
Axial:limb ratio	0.43 (0.178)	0.33 (0.18)	0.1 (0.06)	0.11

Data for continuous variables are presented as mean (SD).
RBD, REM sleep behaviour disorder; UPDRS, Unified Parkinson Disease Rating Scale.

meet the minimal criteria of parkinsonism. Of the excluded patients, mean age was 69.4 (12.2) years, disease duration was 7.7 (6.2) years and UPDRS III was 28.2 (13.1) (none of these values was significantly different from the included group). For various reasons (refusal to tolerate "off" state, enrolment in a study with strict dosing parameters), it was not possible to evaluate four patients in the "off" state. Three patients were taking no PD medications and hence no "on" state evaluation was possible.

Results of polysomnography

Twenty one patients with PD had RBD and 15 did not have RBD; this latter group included two patients with loss of REM atonia without clinical manifestations. Fifteen of the 21 patients with RBD were aware of clinical signs of RBD; of this group, nine reported onset of RBD before PD and six reported RBD onset after PD. No patient had an apnoea/hypopnoea index >20. Seven of 21 patients in the RBD group had excessive daytime somnolence (as defined by a score on the Epworth Sleepiness Scale of ⩾10) compared with four of 15 in the non-RBD group (p = 0.73). There were no differences between the groups in sleep latency, REM latency, total sleep time, sleep efficiency or percentages of stage 1, 2, slow wave and REM sleep.

Basic demographics and disease severity

Patients with RBD tended to be slightly older, were more likely to be male and had a slightly shorter duration of disease, but none of these differences was significant (table 1). Levodopa dose and use of other parkinsonian medications did not differ between the groups. Disease severity measures have been reported elsewhere.[11] To summarise, there was no difference between groups in measures of overall disease severity, including the Hoehn and Yahr and total UPDRS scores (table 1). Among patients with RBD, there was no difference in disease characteristics in patients who developed clinical symptoms of RBD before compared with after cardinal motor manifestations of PD (data not shown).

Motor subtypes

On numerous measures of motor subtype, there were significant differences between patients with PD with and without RBD (table 2). Patients with RBD were less likely to report tremor as the onset symptom, were less likely to be defined as tremor predominant on examination and had a lower proportion of total UPDRS score accounted for by tremor. There was no difference between groups in the proportion of UPDRS accounted for by rigidity, bradykinesia, bulbar dysfunction or

Table 3 Response to medications, motor complications and quantitative motor testing

	RBD (n = 21)	No RBD (n = 15)	Regression RBD main effect (SE)	p Value
Medication on/off differences				
UPDRS II (% change on/off)	7.0 (15.3)	17.2 (27.8)	−0.51 (1.43)	0.72
UPDRS III (% change on/off)	16.2 (18.9)	34.8 (28.2)	−18.5 (9.0)	0.049
Purdue (% change on/off)	4.8 (12.8)	14.8 (20.4)	−6.9 (6.3)	0.29
Up and go (% change on/off)	9.8 (18.3	10.3 (17.5)	−0.70 (6.9)	0.92
Alternate Tap Test (% change)	7.7 (19.4)	16.7 (15.9)	−7.2 (7.0)	0.31
Motor complications of therapy				
History of dyskinesia (yes:no)	4:17 (19%)	5:10 (33%)	0.67 (1.44)	0.64
UPDRS IV (dyskinesia total)	0.52 (1.37)	0.73 (1.28)	0.06 (0.41)	0.89
History of fluctuations (yes:no)	5:16 (24%)	5:10 (33%)	2.0 (1.5)	0.19
UPDRS IV (fluctuations total)	0.62 (1.16)	1.1 (1.5)	−0.20 (0.42)	0.65
Quantitative motor testing				
Purdue Peg "off" (No of pegs)	7.4 (2.1)	8.4 (2.0)	−1.11 (0.64)	0.096
Alternate Tap "off" (No of taps)	132.5 (30.4)	138.1(26.7)	−5.8 (11.0)	0.60
Up and go "off" (s)	10.3 (6.4)	8.8 (2.5)	1.4 (1.8)	0.45

Data for continuous variables are presented as mean (SD).
RBD, REM sleep behaviour disorder; UPDRS, Unified Parkinson Disease Rating Scale.

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gait and no increase in the frequency of choking or drooling. The axial:limb ratio was not significantly different between groups, although there was a trend towards a higher ratio in patients with RBD ($p = 0.11$). More patients in the RBD group reported freezing than in the non-RBD group (38% vs 13%) but this difference was not significant ($p = 0.09$). Finally, a significant difference in the frequency of falls was found; 38% of patients with RBD had experienced falls compared with only 7% in the non-RBD group ($p = 0.04$).

Response to medications, motor complications and quantitative motor measures

Even though there was no difference in levodopa dose or use of other antiparkinsonian agents between the groups, patients with RBD demonstrated a lower amplitude of response to a dose of their usual medication when comparing UPDRS examination in the medication "on" and "off" states (table 3). There were no significant differences in medication response amplitude for quantitative motor measures, although for all three measures the absolute value of the improvement was less in the RBD group. Finally, there was no difference in the frequency or severity of motor fluctuations and dyskinesia between patients with and without RBD. Additionally, there were no differences between groups in any quantitative measure of motor function, including Alternate Tap Test, timed up and go and Purdue Pegboard Testing.

DISCUSSION

We have found that patients with PD with RBD have a disease type that is characterised by less tremor, a higher frequency of falls and a lower amplitude of response to their medication dose. Overall disease severity, motor complications and other motor manifestations did not differ between patients with and without RBD.

To our knowledge, this is the first comprehensive description of motor manifestations of PD in patients with and without RBD that included quantitative motor assessments, motor subtypes and complete examination in the medication "on" and "off" states. There have been some studies that have looked at overall disease severity indices in PD. One recent study examining brainstem spectroscopy in patients with PD found worse UPDRS scores among 12 patients with PD with polysomnography confirmed RBD compared with 12 without a clinical history of RBD.[22] Another study compared UPDRS and tremor versus akinetic rigid subtypes in patients with a clinical history of RBD (no polysomnography confirmation was performed). This study found that patients with RBD had a marginally longer disease duration and higher Hoehn and Yahr scores, but did not find differences in motor subtype.[23] In contrast, a recent study has suggested that patients with clinical symptoms of RBD have lower motor severity scores.[24] One retrospective chart review described UPDRS scores in patients with PD with and without RBD (again assessed only by clinical history), and found that patients with RBD had longer disease duration, higher doses of antiparkinsonian agents and a higher frequency of dyskinesia and fluctuations, although total UPDRS scores were not different.[25] Finally, several studies examining the effect of RBD on visual hallucinations and cognitive impairment in PD[26–28] did not find differences in UPDRS scores. None of these studies adjusted for disease duration or age.

We found that patients with PD with RBD had less tremor predominant disease than those without. This was not universal; three of 21 patients with RBD were tremor predominant. Another recently published study has examined motor subtypes in PD, and also found that patients with RBD had a lower frequency of tremor predominant disease.[29] We also found a higher frequency of falls and a trend towards increased freezing in patients with RBD. In studies of disease prognosis, tremor predominance has been associated with slower progression and better overall prognosis,[2] and falls are commonly considered a marker of increasing disease severity. However, we found no evidence of worse overall motor severity in patients with RBD. Our disease duration was relatively short, so it will be of considerable interest to follow these patients over time; perhaps with longer disease duration, differences in prognosis may appear.

In comparing medication "on" and "off" states, patients with RBD appeared to have less response to medications. This was not due to confounding by different medication use, as use of levodopa and other dopaminergic agents was the same in both groups. Interpretation of this finding is complex, as a lower amplitude of response to a single medication dose can indicate different things. On the one hand, it could suggest that patients with RBD have more levodopa resistant symptoms. The trend towards an increased proportion of axial symptoms and freezing with the increased frequency of falls may support this interpretation, as these symptoms tend to respond less to dopaminergic therapy. On the other hand, patients with RBD could have a preserved long term response to medications, as is typically seen early in disease. Given that we found no significant differences between the groups in terms of markers of disease severity or duration, we cannot tell which of these interpretations is correct. Prospective follow-up of these patients will help to determine the implications of this finding.

In the differential diagnosis of PD, there are several conditions (multiple system atrophy (MSA), progressive supranuclear palsy, vascular parkinsonism, etc) that can also cause parkinsonism. Differentiation of these conditions from PD is based on clinical grounds. RBD is extremely common in MSA in particular (and RBD commonly precedes other manifestations of disease in MSA).[30 31] The features of disease that we found more commonly in patients with RBD, such as absence of robust response to dopaminergic therapy, lack of tremor and falls, are all clues to the fact that an alternate cause of parkinsonism may be present. Therefore, our findings may suggest that the presence of RBD could be a "red flag" for alternate causes of parkinsonism, particularly MSA. Further follow-up of our patients, especially with pathological examination if possible, will allow us to determine if any of our patients with RBD are eventually diagnosed with an alternate condition.

There are some limitations of this study. The breadth of our examination precluded detailed examination of any one feature. We included 36 patients, but a larger study would have more statistical power to find subtle differences between groups. For those items with low frequency (such as psychiatric complications), up to 200 patients would be required to have 80% power to find an effect. Therefore, absence of a significant difference between groups in this study does not rule out modest differences. In particular, there seemed to be a lower rate of RBD in women that was not statistically significant. This is consistent with the well established but as yet unexplained finding that idiopathic RBD is predominant in men—it is not clear whether this gender predominance could be caused by selective presentation (eg, if women have less violent dreams they may be less likely to wake from their RBD episode) or whether sex specific differences in patterns of neurodegeneration in PD exist. It is also important to emphasise that this

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study was not designed to estimate the prevalence of RBD in PD: patients were included from a consecutive sample, and a substantial proportion of patients preferred not to participate. As patients with subjective sleep complaints tended to participate at higher rates than those without, the true prevalence of RBD is probably lower than the proportion of patients with RBD in our study. This study is exploratory in nature, and therefore no correction for multiple comparisons was made; it is possible that some of our findings may have been due to chance. Finally, our evaluation was a single evaluation; we will continue to follow these patients over time, so that prognostic features and disease progression can be assessed prospectively.

The study has several strengths. All patients in our study had a diagnosis of RBD confirmed or refuted by polysomnography. Although this requirement for polysomnography limited study size, we feel that considering the poor sensitivity and specificity of symptom questionnaires for RBD in PD,[7 32] this was an essential step in assuring correct classification of RBD status. Bias was diminished by performing the complete evaluation blinded to the results of polysomnography. Finally, our evaluation was broad and comprehensive, addressing a variety of motor outcomes in both medication ''on'' and ''off'' states.

In summary, we have found that RBD is not an isolated phenomenon in PD. Patients with PD who have RBD tend to have akinetic rigid disease, an increased frequency of falls and less clinical response to medication doses. These findings suggest that RBD, when associated with PD, may indicate a pattern of neurodegeneration that differs from patients without RBD.

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Competing interests: JM received personal compensation as consultant (Boehringer Ingelheim, Servier, Shire Biochem) and speaker (Boehringer, Shire), and received financial support for research activities from Sanofi Synthelabo, GlaxoSmithKline. RBP, JFG, MV and KC have nothing to disclose.

Ethics approval: Ethics approval was obtained from the research ethics board of Hôpital du Sacré Coeur, Montreal, Quebec.

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