Rapid Eye Movement Sleep Behavior Disorder and Risk of Dementia in Parkinson’s Disease: A Prospective Study

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ABSTRACT: One of the most devastating nonmotor manifestations of PD is dementia. There are few established predictors of dementia in PD. In numerous cross-sectional studies, patients with rapid eye movement (REM) sleep behavior disorder (RBD) have increased cognitive impairment on neuropsychological testing, but no prospective studies have assessed whether RBD can predict Parkinson’s dementia. PD patients who were free of dementia were enrolled in a prospective follow-up of a previously published cross-sectional study. All patients had a polysomnogram at baseline. Over a mean 4-year follow-up, the incidence of dementia was assessed in those with or without RBD at baseline using regression analysis, adjusting for age, sex, disease duration, and follow-up duration. Of 61 eligible patients, 45 (74%) were assessed and 42 were included in a full analysis. Twenty-seven patients had baseline RBD, and 15 did not. Four years after the initial evaluation, 48% with RBD developed dementia, compared to 0% of those without (P-adjusted = 0.014). All 13 patients who developed dementia had mild cognitive impairment on baseline examination. Baseline REM sleep atonia loss predicted development of dementia (% tonic REM = 73.2 ± 26.7 with dementia, 40.8 ± 34.5 without; P = 0.029). RBD at baseline also predicted the new development of hallucinations and cognitive fluctuations. In this prospective study, RBD was associated with increased risk of dementia. This indicates that RBD may be a marker of a relatively diffuse, complex subtype of PD.

Key Words: REM sleep behavior disorder; Parkinson’s disease; dementia

One of the most devastating nonmotor manifestations of PD is dementia. Point prevalence of dementia in PD approximates 30%, and 50% experience dementia at 15 years disease duration.1 Dementia is related to disease duration, age, and visual hallucinations and has also been linked to akinetic-rigid subtype, apathy, and depression.1 Other risk factors for dementia are unknown.

Rapid eye movement (REM) sleep behavior disorder (RBD) is a condition characterized by loss of the normal REM sleep atonia, such that patients apparently “act out” the content of their dreams. Approximately 35% to 50% of PD patients have RBD.2 Numerous recent studies have suggested that RBD may be an important marker of a particular disease subtype; RBD in PD has been associated with a predominance of akinetic-rigid signs,3–5 symmetric disease,6,7 increased autonomic dysfunction,8–11 and visual hallucinations.12–16 These differences suggest that RBD may be part of a “diffuse” type of disease, which is characterized, in particular, by more predominant, severe nonmotor symptoms.
In 2007, our group described, in a cross-sectional study, a relationship between cognitive impairment as assessed by neuropsychological testing and the presence of RBD in PD. PD patients with RBD had increased abnormalities of attention-executive function, visuocconstrucional abilities, and episodic verbal memory.17 In 2009, we expanded the cohort, and found that PD patients with RBD had also increased prevalence of mild cognitive impairment (MCI), compared to those without RBD.18 This finding has been confirmed in cross-sectional studies by other groups.13,19 These cross-sectional studies suggest that RBD could be a potential risk factor for dementia in PD. However, this has not been confirmed in prospective studies. Therefore, we conducted a prospective follow-up study of our cohort of PD patients to assess whether the presence of polysomnogram (PSG)-confirmed RBD was associated with increased likelihood of developing dementia.

Patients and Methods

Patients

Patients were recruited from our ongoing PD cohort study assessing sleep in PD.9,18 All patients gave informed consent according to the Declaration of Helsinki. The hospital ethical committee approved the study, and all subjects signed an informed written consent before their participation. Inclusion and exclusion criteria are presented elsewhere10; briefly, all patients had to have a diagnosis of probable PD confirmed by a movement disorders specialist (R.P.) with no dementia at baseline (confirmed by formal neuropsychological testing that included tests of attention/executive function, verbal learning and memory, visuospatial/visuo perceptual functions, and processing speed18). All patients originally enrolled in the cohort study who had a baseline examination between May 2005 and May 2009 (i.e., minimum 2-year follow-up duration) were eligible for follow-up examination. For inclusion, the diagnosis of PD had to be reconfirmed on last follow-up examination, and patients had to have had at least one follow-up examination a minimum of 2 years after the baseline exam.

Diagnosis of RBD

The diagnosis of RBD was established on baseline PSG, according to the criteria of the second edition of the International Classification of Sleep Disorders, as the presence of PSG-confirmed REM sleep without atonia and dream-enactment behavior either on history or on observation during video PSG.20,21 REM sleep without atonia was quantified separately as percent of tonic chin EMG density (cutoff, >30%) and percent of phasic chin EMG density (cutoff, >15%), as recently published,21 and all REM epochs were screened for dream enactment by the technician. Of those with RBD, 27 of 27 had a history of dream enactment at baseline, and 13 of 27 had observed dream-enactment behavior on baseline PSG. On follow-up assessment (but not on baseline assessment), RBD symptoms were assessed by a standardized questionnaire, including the REM sleep behavior disorder Hong Kong Questionnaire (an RBD-HK screening instrument)32 (cutoff for RBD = 19), supplemented by a detailed interview by a movement disorders specialist (R.P.). Patients were interviewed with caregivers/bedpartners, when available, with the caregiver designated as the primary rater.

Diagnosis of Dementia

All patients were offered a neuropsychological examination. Evaluations were carried out between March 2011 and May 2011. Cognitive tests and variables included measures of three main cognitive domains, including attention and executive functions (Digit Span from the Wechsler Adult Intelligence Scale III [scaled score]; a modified version of the Stroop Color Word Test [part III–part I for times or errors]; the Trail Making Test, part B (times); the Semantic verbal fluency test [animals, fruits/vegetables—number of items in 1 minute]), episodic verbal learning and memory (Rey Auditory-Verbal Learning Test [sum of trials 1–5, List B, immediate recall, delayed recall, and recognition]), and visuoconstructional abilities (copy of the Rey-O figure).18 Dementia diagnosis was made according to the Movement Disorders Society (MDS) criteria for PD dementia,23 defined as impairment on ≥2 cognitive domains on neuropsychological testing in association with significant functional impairment from cognitive decline. MCI was defined as the following: (1) a subjective cognitive complaint by patient or informant on the structured interview; (2) objective evidence of cognitive decline, defined as any two scores ≥1.5 standard deviations below the standardized mean in a same cognitive domain (except for the visuoconstructional domain); (3) preserved activities of daily living based on previous and actual capacities; and (4) cognitive deficits not better explained by medication use or another medical or psychiatric disorder.18 If patients refused neuropsychological examination, a systematic questionnaire regarding cognitive symptoms and their effect on an array of daily activities, including the pill questionnaire from the MDS dementia criteria,23 the Mini–Mental State Examination (MMSE),24 and the Montreal Cognitive Assessment (MoCA),25 were performed during clinical examination. For clinical examinations, diagnosis of dementia was established according to the MDS level I dementia criteria (i.e., MMSE <26, impairment of multiple domains, and functional loss resulting from cognitive impairment23) and MCI was diagnosed as
MoCA <26 (after education adjustment) with a subjective complaint of cognitive loss. Visual hallucinations were assessed by semistructured clinical interview and the UPDRS Part I. The presence of fluctuations in cognition was assessed with the Mayo Fluctuations Questionnaire.

**Statistical Analysis**

The primary outcome was the occurrence of dementia (according to MDS dementia criteria) in patients with baseline RBD, compared to those without baseline RBD. Kaplan-Meier’s analysis was used to examine dementia risk according to RBD status. Outcomes were assessed for statistical significance with regression analysis, adjusting for age, sex, disease duration, akinetic/rigid versus tremor-predominant subtype, and duration of follow-up (note that because MCI is predominantly a potential prodromal symptom of dementia, baseline MCI was not included in the regression model).

**Results**

Between May 2005 and May 2009, 61 patients were enrolled in the baseline cohort. Sixteen of sixty-one (26%) could not be evaluated in the follow-up examination; 7 died before follow-up (4 with RBD, 3 without), 5 were lost to follow-up, and 4 refused to be reevaluated and insufficient supplementary information was available (Fig. 1). Therefore, 45 patients (74%) were assessed. Two included patients were ultimately unable to attend in-person clinical evaluation; 1 (non-RBD, no dementia) was hospitalized for acute intercurrent illness before his appointment—the assessment was conducted by telephone with patient and primary caregiver, discussion with treating physician (a movement disorders specialist), and chart review. In the other case (RBD dementia), the patient refused the in-person evaluation, but the diagnosis of dementia had been established on a research-based neuropsychological examination in 2010. After clinical assessment, 3 patients were excluded because an alternate cause for parkinsonism was diagnosed: 1 (RBD and dementia) with multiple system atrophy, 1 (RBD and dementia) with Lewy body dementia (LBD) (disease duration was 6 months at baseline examination), and 1 (without RBD and without dementia) with probable psychogenic parkinsonism. Of the remaining 42 patients, 27 had PSG-confirmed RBD on baseline examination, and 15 did not. Mean follow-up duration was 3.9 ± 1.4 years in the RBD group and 4.1 ± 1.4 years in the non-RBD group (P = 0.73). Thirty had a full level II neuropsychological examination for dementia diagnosis, and 12 (6 with dementia) were diagnosed according to level I criteria. Patient characteristics are outlined in Table 1.

For 27 patients (64%), RBD history was provided by caregivers (20 of 27 with RBD, 7 of 15 without RBD); patients alone provided history in 14 (33%), and no history was available in 1 patient. Of the 15 patients without RBD at baseline, 14 (93%) screened negative on the RBD-HK screening questionnaire and did not have dream-enactment behavior on clinical interview (note, again, that the RBD-HK, published in 2010, was not assessed at baseline). Mean RBD-HK score was 10.0 ± 7.6 in those without baseline RBD, compared to 47.0 ± 16.0 in those with baseline RBD (P < 0.001). One patient had new-onset dream enactment with a RBD-HK score of 25 (cutoff = 19 for probable RBD).

**Cognitive Outcomes According to RBD Status**

As we had previously reported, patients with RBD had a higher prevalence of MCI at baseline (19 of 27 with RBD, 4 of 15 without; P = 0.009). Over the prospective follow-up period, 13 of 42 patients (31%) developed dementia (all had baseline MCI). All of these had RBD at baseline: Therefore, 13 of 27 (48%) of patients with RBD developed dementia, compared to 0 of 15 (0%) of those without (P < 0.001; Fisher’s exact test). Because logistic regression cannot be performed on a perfect relationship (i.e., 0 patients with dementia in the non-RBD group), we performed linear regression for this variable—after adjusting for age, sex, disease duration, duration of follow-up, and motor subtype, the relationship between RBD and dementia was still significant, (P = 0.014) (Table 1). Among RBD patients at baseline, Kaplan-Meier’s analysis (which systematically accounts for censoring and time to event) estimated a 15% risk of dementia at 2 years, 29% at 3 years, and 45% at 4 years, compared to 0% for non-RBD (Fig. 2). Of the 14 patients with RBD without dementia, 7 (i.e., 50%, or 26% of the entire RBD group) had MCI on follow-up assessment. Three patients had developed new-onset MCI, and 4 had MCI on both baseline and follow-up examinations (2 patients with baseline MCI were normal on follow-up).
Of the 15 patients without RBD, 4 (26%) had MCI: 3 were new onset, and 1 had MCI on both baseline and follow-up exams. Therefore, only 7 of 27 (26%) of patients with RBD were free of dementia or MCI, compared to 11 of 15 (74%) of those without RBD ($P = 0.025$). Mean MoCA score at follow-up in those with baseline RBD was 20.1 $\pm$ 6.2, compared to 26.3 $\pm$ 2.3 without ($P = 0.027$). Mean MMSE at follow-up was 24.4 $\pm$ 5.0 in those with RBD, compared to 28.8 $\pm$ 1.8 without ($P = 0.009$). Twelve of twenty-seven patients with baseline RBD had experienced formed visual hallucinations over the last month, compared to 1 of 15 patients without RBD ($P = 0.049$). The mean Mayo Fluctuations score in patients with baseline RBD was 1.27 $\pm$ 1.43, compared to 0.20 $\pm$ 0.78 in those without ($P = 0.012$). Independent of clinical RBD status, quantitative assessment of REM sleep atonia loss at baseline also predicted the development of dementia (percent tonic REM = 73.2 $\pm$ 26.7 with dementia, 40.8 $\pm$ 34.5 without; $P = 0.029$).

Characteristics of Patients With Dementia

Compared to those without dementia, patients who developed dementia were older at baseline (73.1 $\pm$ 5.3 versus 67.8 $\pm$ 9.4). Disease duration was not significantly associated with dementia risk, although point estimates of duration were higher in those with dementia (11.1 $\pm$ 4.5 years vs. 9.0 $\pm$ 4.9; $P = 0.19$). Among RBD patients, neither baseline tonic chin EMG density nor phasic chin EMG density was greater in patients who developed dementia. Between those who developed or did not develop dementia, there was no difference in the proportion of patients whose RBD started before PD diagnosis (50% versus 54%). Of those who developed dementia, 13 of 13 had MCI at baseline (6 single domain, 7 multiple domain), compared to 10 of 29 (8 single domain, 2 multiple domain) who did not develop dementia ($P = <0.001$).

Of patients with dementia, mean MMSE was 21.1 $\pm$ 5.5, and MoCA was 14.4 $\pm$ 5.5. Hallucinations were strongly associated with the presence of dementia (85% experiencing hallucinations versus 7% without dementia; $P = 0.009$). The Mayo Fluctuations Scale was abnormal (3 or greater) in 6 of 12 (50%) patients with dementia (for 1 dementia patient, sufficient history was not available). By contrast, the scale was 3 or greater in 0 of 15 patients without RBD ($P =$ 0.025).
0.003) and in 0 of 14 nondemented patients with RBD (P = 0.004) (Table 2).

Discussion

In this 4-year prospective study, we have found that the presence of RBD predicted the eventual risk of developing dementia in patients with PD. Our findings are broadly consistent with cross-sectional studies demonstrating an association between the presence of cognitive impairment and RBD in PD. In our previous studies, RBD in PD was associated with impaired attention/executive functions, episodic verbal memory, and visuocognitive abilities.17,18 These results have been confirmed by other groups, based upon clinical diagnosis of RBD (i.e., without PSG confirmation).15,19 Similarly, we found a 73% prevalence of MCI in PD patients with RBD, compared to 11% in PD patients without RBD and 8% in healthy controls.18 In one prospective study, patients with hallucinations and clinically probable RBD had more decline on cognitive testing than those without.30 However, this study did not include PSG testing for RBD status and did not compare dementia incidence between RBD and non-RBD patients. A second 2-year prospective study did not find a link between clinical history of RBD at baseline and worsening cognition; however, this was a short follow-up study, did not use PSG confirmation of RBD diagnosis, and was not designed to test cognitive outcomes (including only the MMSE, which is insensitive to cognitive impairment in PD).31 Our findings are also consistent with studies that have suggested that other disease factors possibly associated with dementia risk (e.g., akinetic-rigid subtype and waking EEG slowing) are more common in PD patients with RBD and also with our recent studies that demonstrated an overlap between dementia and parkinsonism in idiopathic RBD patients who progress to a neurodegenerative diagnosis.5,32–34 Our finding that RBD is a risk factor for dementia is consistent with the higher prevalence of MCI in our cross-sectional baseline examination.18 Indeed, all patients with dementia had MCI at baseline. However, as has been previously documented,35,36 the transition from MCI to dementia is not inevitable. Of the 6 patients with RBD and MCI, 2 “reverted to normal” on the follow-up examination (as did 3 of 4 non-RBD patients with baseline MCI).

Of interest, the differences in follow-up MoCA and MMSE between the 14 “RBD-no dementia” patients and those without RBD were relatively modest (MoCA: 26.3 ± 2.3 versus 24.6 ± 3.4, P = 0.17; MMSE: 27.4 ± 1.5 versus 28.8 ± 1.8, P = 0.26). This demonstrates the important advantage of prospective studies—in a cross-sectional study conducted at the second stage, all demented patients would have been excluded, seriously attenuating the difference between groups. This could also suggest that the association between RBD and dementia is present mainly in early- to mid-duration disease (i.e., RBD is primarily a risk factor for conversion to dementia in the first 5-10 years of disease). Note that this subtype would probably be underrepresented in cross-sectional studies, where disease duration exceeds 5 to 10 years, resulting in an underestimation of dementia risk. This would be consistent with other models of PD heterogeneity (based upon cluster analysis of clinical symptoms and upon pathological studies), which describe a relatively aggressive, diffuse subtype of PD that is characterized by early dementia.37,38 These previous cluster-based or pathologic studies did not assess the role of RBD in determining symptom type: Our results suggest that RBD may be a marker of this malignant/complex subtype.
In our previous cross-sectional studies, we saw no
association with hallucinations and RBD status. There was, however, a clear connection evident on
prospective follow-up. The failure to detect a difference in earlier studies is likely the result of short dis-
ease duration in our earlier studies. Our results are
now consistent with numerous studies showing the
connection between RBD and hallucinations in PD. In most cases, the hallucinations occurred
with dementia, underscoring the importance of sys-
tematic assessment of dementia in future studies
assessing hallucinations and RBD. The prevalence of
fluctuations in dementia in our study is similar to that
reported in LBD. As many other groups have dem-
onstrated, age was also a risk factor for dementia in
our study; however, the link between RBD and de-
mentia persists, despite adjusting for age. As would be
expected, we also found that MCI was a strong risk
factor for dementia; all patients developing dementia
had MCI on baseline examination.

Some limitations of this study should be noted.
Although we performed a standardized clinical assess-
ment of RBD, we did not repeat PSG on the second
evaluation; this was mainly because most patients
with dementia would refuse or not tolerate PSG,
resulting in a severe selection bias. As a result, we can-
not prospectively characterize changes in REM sleep
muscle atonia and cannot definitively assess whether
cases, diagnosis is clear. However, for the 6 others
diagnosed as dementia free, a neuropsychological ex-
amination may have been able to detect unrecognized
dementia or MCI (level I evaluation is specific, but is
not prospectively characterzation changes in REM sleep
muscle atonia and cannot definitively assess whether
patients may have developed RBD. Similarly, the
RBD-HK questionnaire has been validated in idiio-
pathic RBD, but not in PD (no RBD questionnaires
have been fully validated in PD). Diagnosis of demen-
tia was based upon a MDS criteria level I clinical eval-
uation in 12 of 42 patients. In many cases, this was
the result of advanced dementia (6 had dementia),
such that patients or caregivers did not feel they could
tolerate the neuropsychological examination; in these
cases, diagnosis is clear. However, for the 6 others
diagnosed as dementia free, a neuropsychologi-

evaluation may have been able to detect unrecognized
dementia or MCI (level I evaluation is specific, but is
less sensitive than level II evaluation). The study was
relatively small, which leads to the imprecision of esti-
mates; obviously, it would be unlikely that larger stud-
ies would not detect any patients without RBD
developing dementia in a 4-year period. Also, follow-
up duration has not yet been conducted to very
advanced disease; we presume that at advanced stages,
many patients (including those without baseline RBD)
will eventually develop dementia. Evolution of RBD
symptoms is difficult to assess and, potentially, could
have been confounded by symptomatic medications;
however, we found no difference in Clinical Global
Impression of Change (CGI-C) scores between those
receiving or not receiving medications. This study
included a higher proportion of males (80%) than the
general PD population (60%–65%); therefore, results
may incompletely generalize to women. Finally, diag-
nosis of PD was clinical, and some patients may have
had alternate diagnoses (such as multiple-system atro-
phy or progressive supranuclear palsy); however,
patients were all examined by a movement disorders
specialist, and residual inclusion of such patients
would not have necessarily attenuated our differences
(as evidenced by our 3 excluded patients, 2 of whom
had RBD and dementia). Finally, note that this study
was a prospective follow-up of a previously described
cross-sectional cohort of patients with PD, many of
whom had MCI at baseline. Predictably, those with
MCI at baseline had a higher risk of dementia. It
would be of interest to assess the role of RBD in the
evolution of both MCI and eventual dementia in a
prospective, long-term study, starting at disease diag-
nosis, in those who do not have MCI at baseline.

Conclusion

In this prospective series of patients with PD, PSG-
confirmed RBD at baseline was a predictor of eventual
development of dementia. This suggests that RBD may
be a marker of a more diffuse, complex disease sub-
type in PD.

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