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# REM Sleep Behavior Disorder in Parkinson's Disease: A Questionnaire-Based Survey

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SCIENTIFIC INVESTIGATIONS

**Study Objectives:** REM sleep behavior disorder (RBD) is reported in up to 50% of patients with Parkinson's disease (PD). Only a few systematic, large-scale studies have addressed the characteristics of RBD in PD. The aim of the present study is to assess the frequency of RBD in patients with PD and the association with PD characteristics.

**Methods:** We sent a questionnaire including items on sleep quality, sleep disorders, and PD characteristics and severity to the members of the national PD patients' organization in Switzerland. To assess and characterize RBD, we used a validated 10-item questionnaire (the RBD screening questionnaire, RBDSQ).

**Results:** Four hundred seventeen PD patients returned the questionnaire, with RBD scores ≥ 6 in 172 patients. These patients had longer disease duration and lower activity of daily living scores, as well as more frequent nighttime awakenings and hallucinations than PD patients with RBDSQ scores < 6. Age, gender, sleep-wake disorders such as excessive daytime sleepiness, sleep apnea, and insomnia, as well as levodopa equivalent dose did not differ between the 2 groups. Patients with RBDSQ score ≥ 6 were more often treated with antidepressants.

**Conclusions:** We confirm a frequent (42.6%) history of RBD in PD. Probable RBD in PD is associated with more advanced disease as suggested by the longer disease duration and higher impairment of daily living. It is also linked to sleep fragmentation with significantly more nighttime awakenings and with hallucinations. Hallucinations might be linked to emotional disinhibition and probably to activation of limbic structures. Both sleep fragmentation and limbic activation might facilitate the occurrence of RBD in PD.

**Keywords:** Idiopathic Parkinson's disease, parasomnias, REM sleep behavior disorder, sleep fragmentation, hallucinations

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REM behavior disorder (RBD) in humans was first described by Schenck et al. in 1986.[1] It is characterized by loss of normal muscle atonia during REM sleep, which leads to increased phasic motor activity and allows dream enactment behavior.[2] Most patients report vivid, frightening dreams, leading to violent behavior, often resulting in injuries of patients or their bed partners.[3] The prevalence of RBD reported in the general population is < 1%,[4,5] whereas in neurodegenerative disorders, especially synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), a much higher frequency is found.[6,7] It has been shown that PSG is the gold standard for the diagnosis of RBD, since only half of the patients are detected by history.[8,9] RBD is reported in up to 47% of patients with PD, based on video-polysomnography (PSG),[8] and REM sleep without atonia (RWA) in up to 58%.[9] It has been suggested that RWA might represent a preclinical form of RBD associated with PD.[9] Until now, several large questionnaire and interview-based studies have addressed RBD in PD, including numbers of 150 to 320 patients.[10-14] In these studies the frequency varied from 27% to 54%, which is close to PSG-based reports.[10-14] As RBD may precede the motor symptoms of neurodegenerative disorder by years,[15-17] there have been multiple attempts to find a questionnaire-based diagnostic tool for RBD. Recently, the REM sleep behavior disorder screening questionnaire (RBDSQ) was developed and validated in German.[18] With a cutoff of 5 points, the questionnaire has a sensitivity of 96% and a specificity of 56% in subjects with sleep-wake disorders and of 92% in control subjects.[18] A validation study of RBDSQ in 75 PD patients with a cutoff of the initially suggested 5 points yielded a sensitivity of 68% and specificity of 63%.[19] In another validation study of RBDSQ in PD patients, a cutoff of 6 points showed much higher sensitivity (84%) and specificity (96%).[20]

In a follow-up polysomnography (PSG) study we tested 10 PD patients with RBDSQ scores ≥ 10. All of them presented with RBD in PSG including RWA and pronounced behavioral peculiarities. We also tested 10 patients with RBDSQ scores ≤ 2. Among them, 5 patients had RWA and gross body jerks in PSG despite the low scores on RBDSQ (unpublished data).

**BRIEF SUMMARY**

**Current Knowledge/Study Rationale:** RBD is very common in PD and there have been multiple attempts to find a questionnaire based diagnostic tool for RBD. For the first time we use a previously validated questionnaire tool assessment of RBD in a large, unselected sample of PD patients.

**Study Impact:** RBD in PD could be detected by a validated questionnaire tool in 42.6% of the patients, which is comparable to the frequency found in PSG-based studies. It was associated with more advanced disease, sleep fragmentation and hallucinations.

**Table 1**—Demographic and clinical characteristics of the study population

| Variable | |
|---|---|
| Age, y | 69 ± 9 |
| Gender, % | 68% men |
| ESS | 10 ± 5 |
| ESS ≥ 10, % | 47 |
| Sleep problem, % | 57 |
| Disease duration, y | 11 ± 7 |
| ADL, % | 76 ± 17 |
| Levodopa equivalent dose, mg | 619 ± 424 |
| COMT inhibitors, % | 27 |
| Amantadine, % | 12 |
| Biperiden, % | 5 |
| MAO-B inhibitors, % | 12 |
| Antidepressants, % | 22 |
| Neuroleptics, % | 8 |
| Benzodiazepines*, % | 14 |
| Dementia medication, % | 3 |

ADL, activities of daily living (Schwab and England); COMT, Catechol-*O*-methyltransferase; ESS, Epworth Sleepiness Scale; MAO-B, monoamine oxidase B. *Including zolpidem/zopiclone.

For the first time we use a validated questionnaire tool in PD patients for assessment of RBD in a large, unselected sample of PD patients. The aim of the present study is to assess the frequency of RBD in patients with PD and the association with PD characteristics.

## METHODS

We sent a questionnaire on sleep-wake disorders and PD characteristics to the members of the national PD patients' organization in Switzerland. The questionnaire was attached to the monthly magazine of the organization. Members of the organization are not only patients with PD but also their caregivers and relatives as well as many physicians. A total of 6,000 surveys were sent, including the French and the Italian speaking parts of Switzerland but the questionnaire was provided only in German. We did not receive information on how many of the recipients are patients. Help of partners and caregivers was accepted but not required for completing the survey. Sleep habits, sleep quality, and sleep-wake disorders were assessed by 17 questions. The answers provide information on symptoms and signs suggestive of obstructive sleep apnea (OSA), excessive daytime sleepiness (EDS), parasomnias, hallucinations, and insomnia. Possible answers include "yes" and "no" or provide a rating on a 5-point scale depending on the frequency of occurrence ("almost always," "often," "occasionally," "seldom," or "never"). As a screening question for restless legs symptoms, we included the single validated question as suggested from the International Restless Legs Syndrome (RLS) Study group.[21,22] EDS and RBD were addressed by validated questionnaires—the Epworth Sleepiness Scale (ESS)[23] and RBDSQ. RBDSQ is a self-rating instrument, consisting of 10 yes-no questions. It assesses the frequency and content of dreams, and their relationship to nocturnal movements and behaviors, self-injuries and injuries of the bed-partner, nocturnal vocalization, sudden limb movements and complex movements during sleep, nocturnal awakenings, disturbed sleep in general, and the presence of neurological disorders. The RBDSQ can be found in **Table S1**. Values > 6 points are considered suggestive for RBD.[20] The questionnaire also assessed PD characteristics, with 6 items gathering information on time of first symptoms, diagnosis and start of treatment, invasive treatment, and type of the PD.

All patients were treated by a general practitioner or a neurologist for Parkinson's disease. All patients allowed us to contact their physicians if confirmation of the diagnosis was needed. To judge the severity of PD, the Schwab and England activities of daily living (ADL) scale was used. The scale estimates a person's ability to perform daily activities in terms of speed and independence through a percentage figure, with 100% indicating total independence, falling to 0%, which indicates a state of complete dependence.[24]

All patients provided a list of their medications. Levodopa equivalent dose (LED) was calculated for each patient.[25]

The study was approved by the local ethics committee, and all patients signed an informed consent, which was attached to the questionnaire.

Statistical analysis was performed using SPSS 15 software. Chi-square, *t*-tests, and Mann-Whitney tests were used to analyze categorical and continuous variables, respectively. The variables, which were significantly different between patients with and without RBD in t-tests and Mann-Whitney tests, were subsequently entered in a binary logistic regression analysis. Significance level was set at $p < 0.05$.

## RESULTS

Four hundred seventeen patients with PD returned the questionnaire. Demographics, clinical characteristics, and treatment of the study population are presented in **Table 1**. Caregiver support for filling in the questionnaire was reported by 61% of the patients. Thirteen patients did not completely fill in the RBDSQ, and were excluded from further analysis. One hundred seventy-two of the remaining 404 patients (42.6%) had an RBDSQ score ≥ 6 (suggestive of probable RBD), and 232 patients had a score < 6. Clinical and demographic characteristics of the 2 groups are presented in **Table 2**.

According to *t*-tests/Mann-Whitney tests a number of variables were significantly different between patients with RBDSQ score ≥ 6 and < 6. However when these variables were entered in a binary logistic regression analysis, only disease duration, ADL score, nighttime awakenings, and hallucinations proved to be significantly different between the 2 groups. RBDSQ scores were equally distributed in men and women. Thirty-six patients reported sleepwalking; 22 of them had a score ≥ 6 on the RBDSQ.

Three hundred ninety-six patients were treated with dopaminergic agents: 129 were on levodopa monotherapy, and 49 on dopamine agonist monotherapy. Five patients received neither levodopa nor dopamine agonists; 2 patients were treated with deep brain stimulation; and 1 underwent stereotactic thalamothomy. Thirteen patients did not provide information

**Table 2**—Demographic and clinical characteristics of groups with and without probable RBD

| Variable | RBD score ≥ 6, n = 172 | RBD score < 6, n = 232 | p (t-test, $\chi^2$, Mann-Whitney test) | p (binary logistic regression) |
|---|---|---|---|---|
| Age, y | 69.5 ± 8.3 | 69.2 ± 9.7 | NS | – |
| Age at PD onset, y | 57.5 ± 10.1 | 59.6 ± 10.8 | NS | – |
| Gender (males, %) | 70% | 66% | NS | – |
| ESS | 11 ± 5.5 | 9.5 ± 5.1 | 0.006 | NS |
| Disease duration, y | 11.7 ± 7.9 | 9.5 ± -6.4 | 0.002 | 0.017 |
| ADL, % | 73 ± 17 | 77 ± 16 | 0.022 | 0.043 |
| LED, mg | 732 ± 392 | 648 ± 367 | 0.042 | NS |
| Night-time awakenings | 2.6 ± 1.3 | 2.2 ± 1.2 | 0.001 | 0.033 |
| Snoring | 2.8 ± 1.2 | 2.5 ± 1.1 | 0.034 | NS |
| Apneas/hypopneas | 1.9 ± 1 | 1.5 ± 0.8 | 0.003 | NS |
| Out of breath at night | 1.7 ± 0.8 | 1.4 ± 0.7 | 0.003 | NS |
| RLS symptoms | 2.5 ± 1.3 | 2 ± 1.2 | < 0.001 | NS |
| Visual hallucinations | 2.1 ± 1.1 | 1.5 ± 0.9 | < 0.001 | 0.002 |

ADL, activities of daily living (Schwab and England); ESS, Epworth Sleepiness Scale; LED, levodopa equivalent dose; PD, idiopathic Parkinson's disease; RBD, REM sleep behavior disorder; RLS, restless legs syndrome.

**Table 3**—Medications in groups with and without probable RBD

| Drug | RBD score ≥ 6, n = 172 | RBD score < 6, n = 232 | p |
|---|---|---|---|
| Dopamine agonist equiv. dose, mg | 214 ± 230 | 206 ± 251 | NS |
| Levodopa equiv. dose, mg | 732 ± 392 | 648 ± 367 | NS |
| COMT inhibitors, n/% | 54/31% | 58/25% | NS |
| Amantadine, n/% | 25/15% | 22/10% | NS |
| MAO-B inhibitors/n, % | 22/13% | 26/11% | NS |
| Biperiden, n/% | 5/3% | 15/7% | NS |
| Antidepressants, n/% | 54/31% | 33/14% | < 0.001 |
| tricyclics, n/% | 16/9% | 10/4% | 0.035 |
| SSRI, n/% | 24/14% | 13/6% | 0.004 |
| mianserin, n/% | 5/3% | 1/0.4% | NS |
| SNRI, n/% | 11/6% | 9/4% | NS |
| Neuroleptics, n/% | 18/10% | 13/6% | NS |
| Cholinesterase inhibitors, n/% | 10/6% | 3/1% | 0.012 |
| Benzodiazepines, n/% | 20/12% | 26/11% | NS |
| Zolpidem/zopiclone, n/% | 6/3% | 5/2% | NS |

COMT, Catechol-O-methyltransferase; MAO-B, monoamine oxidase B; RBD, REM sleep behavior disorder; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin/noradrenalin reuptake inhibitors.

on their therapy. In addition, 36 patients did not provide dopaminergic drugs doses. One hundred sixty three patients with RBDSQ ≥ 6 were treated with dopaminergic agents: 54 of them received levodopa, and 19 received dopamine agonists as monotherapy. The rest of the patients were treated with a combination of levodopa and a dopamine agonist. Dopamine agonist and levodopa equivalent doses (LED), as well as additional medications with possible influence on sleep-wake regulation are presented in **Table 3**. Levodopa and LED were higher in patients with history of RBD according to *t*-tests, yet after entering the data in binary logistic regression analysis, the results were no longer significant. Patients with RBDSQ ≥ 6 were treated more often with antidepressants, including tricyclic antidepressants and SSRIs, as well as cholinesterase inhibitors. Only 13 patients (3 with no history of RBD) were treated with cholinesterase inhibitors.

## DISCUSSION

We used RBDSQ, recently validated in PD patients with a cutoff of 6 points,[20] to identify patients with probable RBD in a large sample of PD patients. Nearly 43% of our patients had a RBDSQ score ≥ 6, suggestive of RBD, which is higher than the frequency reported in most previous history-based studies and close to PSG-based studies.[10-13] Probable RBD in our patient population was associated with nighttime awakenings, hallucinations, longer disease duration, and lower ADL score. In disagreement with other studies, we did not find gender differences between the groups with and without suggested RBD.[13,14] Patients with suggested RBD were more often treated with antidepressants, including tricyclic antidepressants and SSRIs.

In comparison to previous history-based studies,[11-13] our RBDSQ-based study revealed a higher prevalence of RBD in

PD. The combination of items on dream characteristics, nocturnal behaviors, and sleep disturbance may yield a higher sensitivity than previously used methods. In RBDSQ, not only violent movements are addressed, but also gestures and complex movements. Such complex nonviolent motor behaviors were recently described in RBD patients.[26] Including such movements in the score might have increased the sensitivity of the questionnaire. The frequency found in our study is closer to polysomnographic studies[8,9,27] than to most history-based studies. Sixel-Döring et al. confirmed RBD polysomnographically in 46% of their sleep-disturbed PD patients.[27] Interestingly, a similar frequency of RBD was reported by Ondo et al. (43%) based on only one question: "acting out dreams."[10] In this study, however, in 27% of the patients the answer to the question was "not known," which might have led to underestimation of the patients with suggested RBD. Similarly, an even higher frequency of RBD in PD based on history (54%) was found by Yoritaka et al., who studied 150 patients.[14]

A male preponderance has been found not only in idiopathic RBD but also in RBD in PD patients[13,14] in comparison to non-RBD PD patients. Seventy percent of our patients with suggested RBD were male, similar to other reports.[8,12,13,28] Yet no such gender differences have been observed in non-RBD patients.[13,14] In our study, 66% of the non-RBD patients were males; in other words, unlike previous reports we did not find a difference in the male/female ratio between the two groups. One possible explanation is the known slight male preponderance of PD. This finding might also be explained by the assessment of nonviolent behaviors in RBDSQ. Gender differences in dream content and dream enactment behaviors have been described. Whereas men experience both fear and anger in their dreams and have violent nocturnal behaviors, women experience mainly fear and do not act aggressively in their dreams.[29] It is possible that patients with nonaggressive nocturnal behaviors receive less medical attention, which might lead to underestimation of RBD frequency in women. Similar to other studies, we did not find association with age[13,30] or LED.[12,14]

As previously reported,[12,27] our patients with probable RBD had longer disease duration and higher disease severity (as expressed by the ADL score), pointing to more advanced disease.

Tricyclic antidepressants and SSRIs are known to aggravate RBD symptoms in both idiopathic and secondary cases of RBD.[31] Our patients with probable RBD, consistent with previous reports, were treated more often with these drugs compared to patients with no history for RBD according to RBDSQ.

Patients with probable RBD more often reported concomitant sleep disorders such as nighttime awakenings and hallucinations. In agreement with a number of reports,[11,13,14,32-34] we found a higher frequency of hallucinations in patients with probable RBD. This finding may have different explanations:

First, hallucinations and REM sleep disturbance may be attributed to midbrain lesions, as the substantia nigra pars reticulata projects to brainstem nuclei, regulating REM sleep and to limbic structures.[35] Loss of normal muscle atonia may occur due to brainstem lesions, and emotional disinhibition in REM sleep may occur due to the activation of limbic structures.

Second, hallucinations have been linked to cognitive impairment. In PD, though, patients with visual hallucinations may present with, but also without dementia. Harding and Halliday showed that both groups had LB in limbic structures, in particular in the basolateral nucleus of the amygdala.[36] The main difference between the two groups was the absence of neocortical LB in the patients without dementia.[36,37] Based on these findings, they suggested that visual hallucinations and cognitive impairment in PD are likely to have different underlying pathology.[36]

We are aware of the limitations of our study. As this was a postal survey, it is possible that the response rate was higher in PD patients with sleep disorders, thus the high frequency of RBD. On the other hand, previous studies have shown that RBD symptoms often remain undetected by history based tools. As noted in the introduction, we could polysomnographically confirm RBD in 10 PD patients with RBDSQ score $\geq 10$; 5 out of 10 PD patients with RBDSQ score $\leq 2$ had RWA on PSG and gross body jerks with no distinctive abnormal behavior, thus the frequency of RBD in PD may be even higher than suggested by our questionnaire-based findings.

## CONCLUSION

Probable RBD in PD is associated with more advanced disease, as suggested by longer disease duration and higher impairment of daily living. It is also linked to sleep fragmentation (with patients with probable RBD reporting significantly more nighttime awakenings) and to hallucinations. Hallucinations might be linked to emotional disinhibition and to activation of limbic structures. Both sleep fragmentation and limbic activation might facilitate the occurrence of RBD in PD.

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## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

## SUPPLEMENTAL MATERIAL

**Table S1**—RBDSQ: (adapted from Stiasny-Kolster et al., 2007[18])

| N | Question | Answer |
|---|---|---|
| 1. | I sometimes have very vivid dreams. | yes/no |
| 2. | My dreams frequently have an aggressive or action-packed content. | yes/no |
| 3. | The dream contents mostly match my nocturnal behaviour. | yes/no |
| 4. | I know that my arms or legs move when I sleep. | yes/no |
| 5. | It thereby happened that I (almost) hurt my bed partner or myself. | yes/no |
| 6. | I have or had the following phenomena during my dreams: | |
| 6.1. | speaking, shouting, swearing, laughing loudly | yes/no |
| 6.2. | sudden limb movements, "fights" | yes/no |
| 6.3. | gestures, complex movements, that are useless during sleep, e.g., to wave, to salute, to frighten mosquitoes, falls off the bed | yes/no |
| 6.4. | things that fell down around the bed, e.g., bedside lamp, book, glasses | yes/no |
| 7. | It happens that my movements awake me. | yes/no |
| 8. | After awakening I mostly remember the content of my dreams well. | yes/no |
| 9. | My sleep is frequently disturbed. | yes/no |
| 10. | I have/had a disease of the nervous system (e.g., stroke, head trauma, parkinsonism, RLS, narcolepsy, depression, epilepsy, inflammatory disease of the brain), which? | yes/no |