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# The effect of REM sleep behaviour disorder on clinical severity in Parkinson's disease

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**Aim:** Differently from previous studies that directly compared Parkinson's disease (PD) patients with and without rapid eye movement (REM) sleep behavioural disorder (RBD) for the stage, severity, and duration of disease, this study investigated the relationship between the duration and clinical severity of disease in PD patients with and without RBD.

**Materials and methods:** This retrospective study consisted of 141 PD patients older than 18 years of age. The clinical diagnosis of RBD was based on the minimal diagnostic criteria of the revised 2001 *International Classification of Sleep* Disorders. The patients were divided into 2 subgroups, those with and without clinical RBD. The groups were then compared with each other for sex, age, the duration of disease, and the Hoehn and Yahr stage and Unified Parkinson's Disease Rating Scale scores. The correlation between the duration of disease and the clinical severity of PD was analysed in all patients.

**Results:** There was no significant difference between the groups in terms of sex, age, disease duration, and clinical severity scores. For the RBD patients there was a weak positive correlation between the duration of PD and clinical severity scores. However, there was no such correlation in the non-RBD (NRBD) subgroup.

**Conclusion:** Our study indicates that in PD patients with RBD compared with NRBD patients, the time taken to reach the same clinical severity scores may be shorter.

**Key words:** Parkinson's disease, REM sleep behavioural disorder, clinical severity, the duration of Parkinson's disease, the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr stage

## Introduction

Rapid eye movement (REM) sleep behavioural disorder (RBD) is characterised by the presence of abnormal body and limb movements such as hitting, and vocalisations such as talking, shouting, crying, and laughing. These are associated with dream mentation due to a loss of muscle atonia during REM sleep (1-4). It has been reported that RBD is seen in up to two-thirds of patients with Parkinson's disease (PD) (5). There is evidence that PD patients with RBD have a more nontremor predominant type (6) and more nonmotor symptoms than those without RBD (7); therefore, they exhibit a worse prognosis. Emre et al. (7) reported that RBD is a risk factor for developing PD dementia. Many studies have demonstrated that PD patients with RBD had longer disease durations and higher clinical severity scores (1,3,5,8). Contrary to these studies, a recent study (9) reported that there was no difference between PD patients with and without RBD in regards to the initial motor symptoms, duration, and Hoehn and Yahr (HY) stage of the disease, and the development of dementia. Thus, the relationship between RBD and other clinical features of PD such as PD dementia, duration, stage, and severity of disease has remained controversial. On the other hand, in previous studies,

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patients with and without RBD had differing disease durations. It is very important to consider the duration of disease in the assessment of the clinical severity of PD, because PD is a progressive disease.

In contrast to the previous studies that directly compared patients with and without RBD for the stage, severity, and duration of disease, we investigated the relationship between the duration and clinical severity of PD in patients with and without RBD. Our hypothesis was that for similar disease durations, PD patients with RBD may have higher Unified Parkinson's Disease Rating Scale (UPDRS) scores and HY stages than those without RBD.

## Materials and methods

This retrospective study was approved by the local ethics committee of our university. Patients with PD who were older than 18 years of age (n = 147) and who attended the neurology clinic of the university hospital during the period between November 2008 and September 2010 were chosen for inclusion in this study.

Since November 2008, in our polyclinic, PD patients have been examined by a neurologist (D.A.) who is experienced in movement disorders. For each patient, a detailed history of motor and nonmotor symptoms (including RBD) of PD was obtained, and the clinical condition was rated with the HY and UPDRS (motor/total) scores assessed in the 'ON' state. All of the following clinical signs associated with RBD were noted in their history: talking, crying out, swearing, laughing, shouting, waking the partner, physical restlessness, punching, kicking, hitting, and falling out of bed while asleep.

The clinical diagnosis of RBD was based on the minimal diagnostic criteria of the 2001 revised *International Classification of Sleep Disorders* (ICSD-R), which included limb or body movements associated with dream mentation and at least one of the following: harmful or potentially harmful sleep behaviours; dreams that appear to be "acted out"; or sleep behaviours that disrupted sleep continuity (1,3,5,8-10).

Diagnosis of PD was based on the United Kingdom Brain Bank's criteria as bradykinesia in association with rest tremor, rigidity, or postural instability (11).

All of these data from the PD patients had been recorded in a computer program and were reanalysed for this study. The patients were divided into 2 subgroups, those with and without clinical RBD. Patients were called by a researcher (A.A.) for their latest clinical status.

All PD patients with and without clinical RBD were included in this study. Exclusion criteria were as follows: 1) single patients; 2) patients whose disease duration could not be determined with any certainty; 3) patients without a good history (e.g., partner's report) of the motor behaviour and vocalisations during REM sleep; 4) patients whose HY stage and UPDRS scores in the 'ON' state could not be determined; and 5) patients whose duration and clinical severity (i.e. HY stage and UPDRS scores) of PD could not be determined simultaneously.

### Statistical analysis

Statistical analysis was performed by Y.B. The results were analysed using SPSS 15.0. $P < 0.05$ was considered statistically significant in all tests. Because the data were nonnormally distributed, the statistical analysis was performed using nonparametric tests (i.e. Mann-Whitney and chi-square tests) to compare variables of the 2 groups in our study.

Groups 1 (patients with RBD) and 2 (non-RBD patients; NRBD) were compared to each other for sex, age, the duration of disease, and the HY stage (both overall stage score and any score of >2) and UPDRS scores. A regression correlation test was used to analyse the correlation between the duration of and the clinical severity (i.e. UPDRS and HY stage scores) of PD in all patients.

## Results

The study excluded 6 out of the 147 recruited patients because they met the exclusion criteria. Thus, 141 PD patients were assessed according to the ICSD-R minimal clinical diagnostic criteria for RBD. For the 141 PD patients (91 men, 50 women), the mean age at admission was 66.36 ± 10 years. There were 90 patients with RBD (64%) and 51 patients without RBD (36%). The mean age at admission was 65.00 ± 12 years in the NRBD group and 67.14 ± 9.9 years in

the RBD group. There was no significant difference among the RBD and NRBD groups in terms of sex and mean age (P = 0.604; df = 1 and P = 0.416, respectively; Table).

The mean duration of disease did not differ between the subtypes (5.7 ± 5 versus 5.1 ± 4, P = 0.451; Table). The mean UPDRS scores (total/motor) were 39.94 ± 20/23.6 ± 12 in the RBD group and 35.82 ± 25/22.15 ± 14 in the NRBD group (P = 0.057 and P = 0.200, respectively; Table). A stage score of >2 was significantly more common in the RBD group than in the NRBD group (64.4% versus 45.1%, P = 0.04; df = 1; Table). Figure 1 shows the relation between the duration of PD and the HY stage score in the RBD and NRBD subgroups. For the RBD patients, there was a weak positive correlation between the duration of PD and the HY stage score (r = 0.319; P = 0.002; $r^2$ = 0.102). Similarly, there was a weak positive correlation between the duration of PD and UPDRS (motor and total) scores in the RBD group (r = 0.309, P = 0.003, and $r^2$ = 0.095; r = 0.296, P = 0.005, and $r^2$ = 0.087, respectively; Figures 1 and 2). There was no correlation between the duration of PD and clinical severity scores in the NRBD subgroup (Figures 1-3).

## Discussion

In the literature, there are studies comparing RBD and NRBD groups of PD patients for demographic features, disease duration, UPDRS scores, and HY stages (3,5,6,8,9,12). Lee et al. (5) reported that patients with RBD had a longer duration of PD symptoms and higher UPDRS scores and HY stages compared to those without RBD. Yoritaka et al. (9) demonstrated that the duration of PD was significantly longer in patients with RBD than those without (P = 0.013), but there was no difference between RBD and NRBD patients for mean stage scores (3.0 ± 0.6 and 2.8 ± 0.6, respectively; P = 0.05). Scaglione et al. (3) reported that RBD patients had longer disease duration and higher HY stage scores than NRBD patients. Gjerstad et al. (8) found that disease duration was longer (11.1 years) in RBD patients than in NRBD patients (8.6 years). In their study, the motor and stage scores of RBD patients, compared with NRBD patients, were also higher (8). In a study using polysomnography, patients with RBD were compared with those without RBD, and the RBD patients' UPDRS scores were higher (12). Contrary to other studies, Postuma et al. (6) found no significant differences in regards to disease duration and UPDRS scores between NRBD patients and patients who had polysomnography-confirmed RBD. Thus, in the literature, the data from studies comparing RBD and NRBD groups for disease duration, UPDRS, and HY stage are inconsistent. In these studies, it has also been seen that patients with and without RBD, compared for the clinical severity of PD, have different disease durations. In contrast to previous studies, we assessed the relationship between disease duration and the clinical severity of PD in the RBD and NRBD groups. In this study, in the RBD subtype the duration of PD was correlated with both the UPDRS scores (total/motor) and the stage of disease.

Table. Clinical features of PD in the RBD and NRBD subtypes of PD.

| Features | | Subtypes | | P |
|---|---|---|---|---|
| | | RBD (n = 90) | NRBD (n = 51 ) | |
| **Male** | % (n) | 66.7 (60) | 60.8 (31) | NS |
| **Female** | % (n) | 33.3 (30) | 39.2 (20) | NS |
| **Age (years)** | Mean ± SD | 67.14 ± 9.9 | 65.00 ± 12 | NS |
| **UPDRS III** | Mean ± SD | 23.6 ± 12 | 22.15 ± 14 | NS |
| **UPDRS Total** | Mean ± SD | 39.94 ± 20 | 35.82 ± 25. | NS |
| **Hoehn and Yahr score of >2** | % (n) | 64.4 (58) | 45.1 (23) | 0.04 |
| **Disease duration (tears)** | Mean ± SD | 5.7 ± 5 | 5.1 ± 4 | NS |

NS: Nonsignificant; UPDRS III: Unified Parkinson's Disease Rating Scale section III; RBD: rapid eye movement (REM) sleep behavioural disorder.

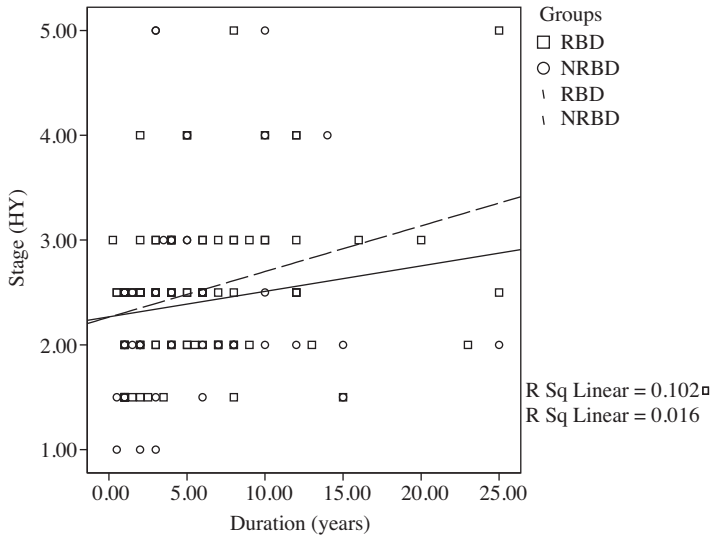


Figure 1. The relation between the duration of PD and the HY stage. Linear regression analysis was performed separately in the RBD ($r = 0.319$; $r^2 = 0.102$; $P = 0.002$) and NRBD ($r = 0.125$; $r^2 = 0.016$; $P = 0.303$) patients.

However, this correlation was not seen with the NRBD subtype. Thus, we found higher UPDRS scores and HY stages in the RBD patients compared with NRBD patients who had the same disease duration. This status may be related to the evidence that RBD patients have more motor and nonmotor symptoms and, accordingly, a more widespread involvement of the central nervous system (CNS) structure for the same disease duration. These results may indicate that RBD patients exhibit a more rapid progression

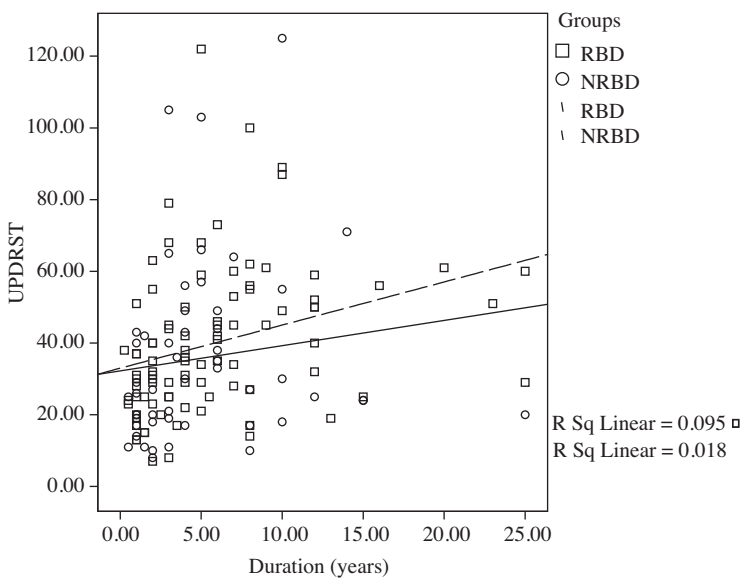


Figure 2. Regression analysis of UPDRS total (UPDRST) score versus duration in the subgroups. The intermittent line represents the RBD group and shows a correlation of increasing UPDRST scores with increasing duration ($r = 0.309$; $r^2 = 0.095$; $P = 0.003$). However, in the NRBD group (solid line), there was no correlation of UPDRST scores with duration ($r = 0.134$; $r^2 = 0.018$; $P = 0.347$).

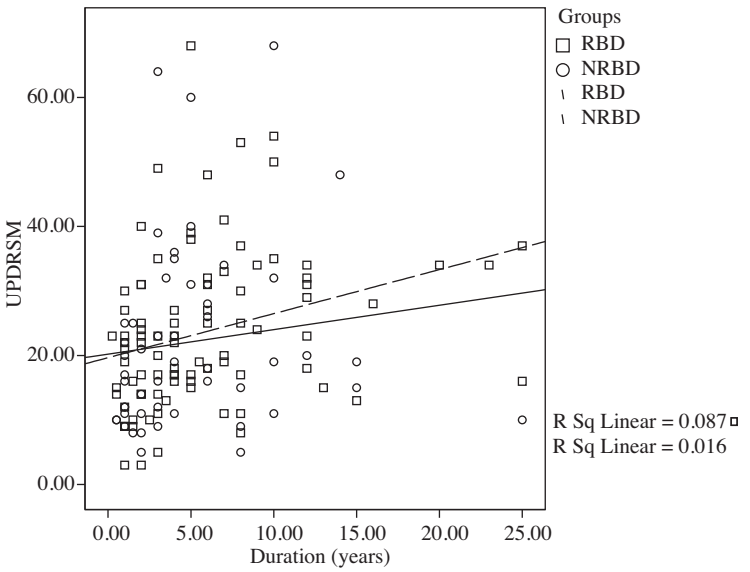


Figure 3. Regression analysis of UPDRS motor (UPDRSM) score versus duration in the subgroups. The intermittent line represents the RBD group and shows a correlation of increasing UPDRSM scores with increasing duration ($r = 0.296$; $r^2 = 0.087$; $P = 0.05$). However, in the NRBD group (solid line), there was no correlation of UPDRSM scores with duration ($r = 0.125$; $r^2 = 0.016$; $P = 0.383$).

of PD than NRBD patients. In our study, a stage score of >2 was significantly more common in the RBD group than the NRBD group (64.4% versus 45.1%; P = 0.04; df = 1). However, the duration of PD was not different between the subtypes (mean: 5.7 ± 5 versus 5.1 ± 4; P = 0.451). The last 2 findings also suggest that RBD patients have a worse prognosis than those with the NRBD subtype. The relation to parkinsonian degeneration in the brainstem nuclei regulating REM sleep of RBD is well known (2). It is believed that the pathophysiology of RBD involves the nucleus reticularis magnocellularis and peri-locus coeruleus in the pons and the pedunculopontine nucleus in the mesopontine area (1,13-15). It has been suggested that RBD may precede the onset of motor symptoms (1,2,3,8,16). The Braak staging theory suggests that neuronal degeneration (i.e. Lewy body pathology) begins in the medulla and progresses upwards (e.g., to the neocortex) in PD (17). According to this theory, RBD corresponds to the second-stage of Braak, followed by the motor signs of PD (13,17). The motor signs of PD occur when the substantia nigra (Stage 3) is affected (17). On the other hand, it has been reported that RBD is associated with an increased risk of the development of other nonmotor symptoms (7,18). This may indicate that when RBD patients develop PD, they have a more widespread involvement of the CNS structures than in those without RBD, including the areas responsible for RBD in the brainstem. Therefore, it is possible that PD patients with RBD have an increased number of motor and nonmotor symptoms associated with the increased clinical severity of PD, as suggested in many studies (5,8,9). Finally, these results may indicate that the time taken to progress from the onset of motor symptoms to disability will be shorter in PD patients with RBD than in those without RBD.

The most important limitation of this study was the use of the ICSD-R minimal diagnosis criteria without polysomnography to diagnose RBD. The new diagnostic criteria of RBD, according to the ICSD 2005, requires polysomnographic documentation of normal skeletal muscle atonia loss in REM sleep (4,19). However, many recent studies of PD have used the ICSD-R minimal diagnostic criteria and do not require a polysomnographic examination for the clinical diagnosis of RBD, as in the present study (3,5,8,9).

Our study indicates that in PD patients with RBD, compared to those without RBD, the time taken to reach the same clinical severity scores may be shorter. Thus, in PD patients with RBD the disease may have a more rapid progression; hence, they have a worse prognosis than those without RBD.

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