



Apathy in Parkinson's disease with REM sleep behavior disorder

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ABSTRACT

Objectives: Rapid eye movement (REM) sleep behavior disorder (RBD) in patients with Parkinson's disease (PD) is associated with increased risk of non-motor symptoms. However, the association between RBD and apathy in PD remains unclear.

Aims: To compare the prevalence and severity of apathy symptoms in PD patients with RBD (PD-RBD+) and without (PD-RBD-). In addition, we explored the association between apathy, depressive symptoms and RBD, taking into consideration the concomitant influence of demographic, disease- and therapy-associated variables. **Methods:** Sixty-four PD patients were evaluated with systematic motor (unified Parkinson's disease rating scale, UPDRS-III) and non-motor assessments. The diagnosis of RBD was based on the international consensus criteria using video-polysomnography. Apathy, sleepiness, depressive symptoms and cognitive performance were assessed using the Starkstein apathy (SAS, cut-off = 14), the Epworth sleepiness (ESS), the Hamilton depression (HAM-D, cut-off = 9) scales and the mini-mental state examination (MMSE), respectively.

Results: Among 64 patients, 26 (40%) had RBD. In the PD-RBD+ group, apathy symptoms were more frequent (52% vs 42%) and more severe (14.3 ± 5.8 vs 11.2 ± 4.9 , $p < 0.05$), especially in the females (17.3 ± 6.0 vs 11.4 ± 5.8 in males, $p < 0.05$) compared to the PD-RBD- group. A high percentage of patients, especially in the PD-RBD+ group (53%), had isolated apathy without increased depressive symptoms. Increased depressive symptoms were also more frequent (50% vs 20%) and more severe in the PD-RBD+ group. The two groups were comparable in respect to demographic and clinical characteristics.

Conclusions: In PD, RBD is associated with isolated apathy and increased severity of depressive symptoms, independent of medication, motor and other non-motor symptoms. Potential mechanisms underlying this association are discussed.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM parasomnia characterized by the loss of normal skeletal muscle atonia during REM sleep with prominent motor activity and (oft frightening) dreaming [1,2]. RBD can be found in up to 50% of Parkinson's disease (PD) patients and often precedes parkinsonian motor signs by several years [3,4]. There is evidence that, apart from the characteristic nocturnal behaviors, PD patients with RBD experience more non-motor symptoms than PD patients without RBD [5–8]. Indeed, RBD in PD patients is associated with cognitive alterations, daytime sleepiness, sleep disturbances including the presence of other parasomnias, psychiatric manifestations, and hallucinations [5,6]. In addition, PD patients with RBD report increased levels of mood disturbances such as

depression and anxiety compared to PD patients without RBD [7,8].

Apathy is defined as lack of motivation, relative to the individual's previous level of functioning, and is manifested by a reduced interest, lack of initiative, diminished goal directed cognition and behavior, and a flattening of affect [9]. Although apathy overlaps conceptually and clinically with other behavioral and psychological features, such as depression, it is considered a distinctive symptom [10].

Apathy is highly prevalent in PD and has negative implications for treatment and long-term outcome of the disease by impacting the overall level of handicap and the quality of life of the patients [11,12]. Apathy is often reported to be present in the very early, even in the premotor, phases of the disease [13]. Indeed, a recent study reported increased apathy and depression in patients with idiopathic RBD [14], a condition which is considered to be a prodromal marker of PD [15]. To

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the best of our knowledge, there are no studies on the association between apathy and RBD in PD patients.

The main aim of our study was to investigate whether the presence of RBD in PD patients is associated with increased risk of apathy. Further, we explored the association between apathy, severity of depressive symptoms and RBD in PD patients, taking into consideration the influence of demographic as well as disease- and therapy-associated variables.

2. Patients and methods

The protocol for this retrospective study was approved by the local ethics committee (Kantonale Ethikkommission Bern, KEK-BE 2016–00369).

2.1. Patients

We retrospectively analyzed data from 64 subjects with PD [16] who underwent a multimodal motor and non-motor assessment prior to deep brain stimulation (DBS) (inclusion and exclusion criteria for DBS as previously published [17]) at the University Hospital Bern from 2012 to 2016. Subjects were grouped according to the presence or not of RBD. We confirmed RBD diagnosis by video-polysomnography documenting the loss of motor atonia during REM sleep and corresponding behaviors based on the international diagnostic criteria [18]. At the time of the assessments, patients were receiving their regular treatment.

2.2. Motor assessments

The motor assessment included the modified Hoehn & Yahr (H&Y) stage and the unified Parkinson's disease rating scale (UPDRS parts I-IV) in "on" and "off" dopaminergic medication.

2.3. Non-motor assessments

We assessed apathy using the Starkstein apathy scale (SAS). The scale contains 14 items phrased as questions using a four-point Likert scale. The total score ranges from 0 to 42, with higher scores indicating greater apathy. A SAS score of ≥ 14 is suggestive of significant apathy [11].

The Hamilton depression rating scale (HAM-D) was used to evaluate the severity of depressive symptoms. For screening purposes in PD patients, a cut-off score of 9 for increased depressive symptoms has been suggested [19].

The Epworth sleepiness scale (ESS) provides a measurement of the patient's subjective habitual level of daytime sleepiness, respectively how likely participants fall asleep in different situations. It consists of 8 items with a 4-step scale. ESS is recommended for use in patients with PD [20]. Excessive daytime sleepiness is defined as an ESS score ≥ 10 (total score range 0–24).

Our standard pre-DBS program includes a detailed semi-structure neuropsychological/cognitive assessment, including the Mini-Mental State Examination (MMSE), for the detection of mild cognitive impairment or dementia (exclusion criterion for DBS surgery), since the MMSE alone does not have adequate psychometric properties as a screening instrument in PD patients [21]. In this study, MMSE score is used to estimate the severity of cognitive impairment [22].

2.4. Statistical analysis

We compared the mean values between groups using the non-parametric Welch's *t*-test. In addition, we performed bivariate correlation analysis to identify variables related to apathy. Two-tailed statistical significance level was set at $p < 0.05$.

For the statistical analysis and graphs, SPSS-18 and Prism 7.01 for Windows (GraphPad Software, Inc., San Diego, CA, USA) were used.

Table 1

Demographic and clinical characteristics of PD patients with and without RBD.

	PD-RBD- (Mean \pm SD) N = 38	PD-RBD+ (Mean \pm SD) N = 26	p
Age	63.0 \pm 9.4	62.6 \pm 7.7	ns
PD years	11.4 \pm 4.8	12.8 \pm 4.2	ns
UPDRS_II (ON)	8.0 \pm 3.4	9.1 \pm 4.3	ns
UPDRS_II (OFF)	13.7 \pm 5.2	18.0 \pm 8.4	*
UPDRS_III (ON)	13.7 \pm 5.2	15.2 \pm 7.8	ns
UPDRS_III (OFF)	32.4 \pm 9.7	38.2 \pm 19.0	ns
UPDRS_IV	7.5 \pm 3.4	7.7 \pm 3.3	ns
H&Y (OFF)	2.9 \pm 0.6	2.8 \pm 0.5	ns
LEDD	1157 \pm 623	1110 \pm 483.8	ns
Use of antidepressants (%)	32%	36%	ns

PD, Parkinson's disease; RBD, REM sleep behavior disorder; UPDRS, unified parkinson's disease rating scale; H&Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; SD, standard deviation; ns, non-significant.

* $p < 0.05$ in Welch's Test.

3. Results

The study included 64 PD patients. Among them, 26 (40%) fulfilled the clinical and polysomnographic criteria for RBD, while 38 had no RBD. The two groups, PD patients with RBD (PD-RBD+) and PD patients without RBD (PD-RBD-), were comparable with respect to age and PD duration. The mean UPDRS-II score was significantly higher in the PD-RBD+ group, while the mean score for the H&Y and the UPDRS-III did not differ significantly between the two groups. The baseline characteristics of our cohort were comparable to other DBS cohorts [23]. Table 1 presents demographic and clinical characteristics for both groups.

Among the subjects in the PD-RBD+ group, 52% had increased apathy (SAS ≥ 14) and 50% had increased scores in the depression rating scale (HAM-D ≥ 9). In the PD-RBD- group, increased apathy and depressive symptoms were found in 42% and 20% of the patients respectively. Subjects in the PD-RBD+ group had significantly higher mean SAS and HAM-D scores than subjects in the PD-RBD- group (Fig. 1) but they had comparable mean scores in ESS and MMSE (Table 2).

In our cohort, 53% of non-depressed subjects in the PD-RBD+ group and 29% in the PD-RBD- group had an increased apathy score. Similarly, 58% of subjects in the PD-RBD+ group and 64% of subjects in the PD-RBD- group had increased depressive symptoms but not increased apathy score. The differences between PD-RBD- and PD-RBD+ in respect to apathy score were more significant among females compared to males (Table 3).

In the PD-RBD+ group, females had higher apathy scores than

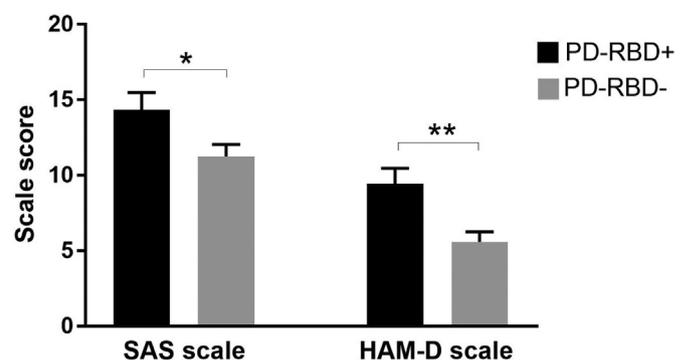


Fig. 1. Apathy and depression score in PD patients with and without RBD. SAS, Starkstein apathy scale; HAM-D, Hamilton depression scale; PD-RBD+, Parkinson's disease with RBD; PD-RBD- Parkinson's disease without RBD. Error bars represent standard error of the mean (SEM).

* $p < 0.05$, ** $p < 0.01$.

Table 2
Mean values of several non-motor scales in PD patients with and without RBD.

	PD-RBD- (Mean ± SD) N = 38	PD-RBD+ (Mean ± SD) N = 26	P
ESS	8.8 ± 4.7	8.2 ± 3.5	ns
SAS	11.2 ± 4.9	14.3 ± 5.8	*
HAM-D	5.6 ± 4.1	9.4 ± 5.1	**
MMSE	27.8 ± 2.6	28.4 ± 1.5	ns

ESS, Epworth Sleepiness Scale; SAS, Starkstein Apathy Scale; HAM-D, Hamilton Depression Scale; MMSE, mini-mental state examination; SD, standard deviation; ns, non-significant.

Mann-Whitney Test, significant difference *p < 0.05 and **p < 0.01, two-tailed.

males but this difference did not reach significance. We found no other gender-related differences with respect to motor and other non-motor symptoms (Table 3). Antidepressant use in the PD-RBD+ group was more common among females than males but the difference did not reach significance (p = 0.07). Gender was the only independent predictor of apathy in the PD-RBD+ group, with women presenting a higher risk compared to men (Table 4).

4. Discussion

In this study, we compared the prevalence and severity of apathy in PD patients with and without RBD. The two groups were comparable in respect to age, disease duration, motor symptoms (UPDRS-III), disability (UPDRS-II) and H&Y score. We report for the first time that RBD in PD patients is associated with apathy, both isolated apathy or apathy in combination with depressive symptoms. In the PD-RBD+ group, apathy symptoms were more frequent and more severe, especially in the females, than in the PD-RBD- group. Noteworthy, the frequency and the severity of depressive symptoms were significantly higher in patients with PD and RBD than in patients without RBD. Our results are consistent with previous studies showing that the presence of RBD in individuals with PD is an important clinical risk factor for increased non-motor symptoms including cognitive, sleep-wake, neuropsychological and psychiatric manifestations [5–8]. Consequently, PD patients with apathy and depressive symptoms should be clinically screened for the presence of RBD.

Apathy is a frequent and clinically relevant impairment of motivation and goal-directed behavior in PD mainly due to the important role of dopamine in neural pathways underlying goal-directed behaviour and reward [13]. In PD, it has been associated with the denervation of ascending mesostriatal, mesolimbic, and mesocortical dopaminergic pathways [24]. A recent study reported increased apathy and depression in patients with idiopathic RBD [14], a condition which is considered to be a prodromal marker of PD [15]. The pathological substrate of apathy in RBD remains unclear. However, it might be associated with the different neurochemical and neuroanatomical

Table 3
Gender differences among PD patients with and without RBD in respect to motor, non-motor scales and disease features.

	Females			Males		
	PD-RBD- (Mean ± SD)	PD-RBD+ (Mean ± SD)	p	PD-RBD- (Mean ± SD)	PD-RBD+ (Mean ± SD)	p
UPDRS_III_ON	12.9 ± 5.4	17 ± 8.4	ns	14.5 ± 5.2	14.4 ± 7.6	ns
UPDRS_III_OFF	33.9 ± 10.0	41.5 ± 20.4	ns	30.8 ± 9.3	36.8 ± 18.9	ns
H&Y_OFF	3.0 ± 0.6	2.8 ± 0.7	ns	2.7 ± 0.5	2.8 ± 0.4	ns
LEDD	934 ± 347	1287 ± 441	ns	1445 ± 811	1033 ± 495	ns
SAS	11.4 ± 5.8	17.3 ± 6.0	*	11.2 ± 4.0	13.2 ± 5.5	ns
HAM-D	5.2 ± 3.1	7.9 ± 3.6	ns	6.0 ± 4.9	10.0 ± 5.9	ns
ESS	9.4 ± 4.9	6.8 ± 4.0	ns	8.2 ± 4.5	8.7 ± 3.1	ns

PD, Parkinson's disease; RBD, REM sleep behavior disorder; UPDRS, unified parkinson's disease rating scale; H&Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; SAS, Starkstein apathy scale; HAM-D, Hamilton depression scale; ESS, Epworth sleepiness scale; SD, standard deviation; ns, non-significant.

* p < 0.05.

Table 4
Association of clinical characteristics and apathy score in PD patients with RBD.

	SAS			
	β ^a	SE β	β	p
Gender	5.0	2.70	0.39	*
HAM-D	0.34	0.25	0.29	ns
UPDRS_III_OFF	-0.12	0.07	-0.34	ns
H&Y_OFF	1.50	1.49	0.21	ns

SAS, Starkstein apathy scale; HAM-D, Hamilton depression scale; UPDRS, unified parkinson's disease rating scale; H&Y, Hoehn and Yahr scale; ns, non-significant.

* p values < 0.05 were regarded as significant.

^a Unstandardized beta coefficients.

patterns of degeneration that have been reported in patients with RBD in the premotor and motor phase of PD [25]. In a recent study, authors investigated regional cerebral blood flow changes using single photon emission computed tomography (SPECT) in patients with RBD and demonstrated functional brain abnormalities mainly in limbic structures, which are known to be involved in motivation, emotion and mood [26]. In addition, RBD as PD comorbidity has been associated with a prominent loss of volume and atrophy in several subcortical and cortical regions, including important limbic structures such as the amygdala and the anterior cingulate, which are also dysfunctional in apathy [13,25]. Recently, Sommerauer et al. based on MRI and 11C-MeNER (a marker of noradrenaline transporter) PET data, showed that PD patients with RBD had decreased locus coeruleus neuromelanin signal on MRI and widespread reduced noradrenaline transporter availability, compared to PD patients without RBD [27]. Previous studies reported increased locus coeruleus pathology in depressed compared to non-depressed PD patients, suggesting the involvement of the locus coeruleus and the noradrenergic system in neuropsychiatric symptoms in PD patients [28,29]. The above data suggest that in addition to limbic structures and dopaminergic degeneration, other structures and underlying neurochemical mechanisms seem to be associated with apathy in RBD. Our findings with increased apathy and depression in the subgroup of PD patients with RBD may reflect the clinical outcome of the different neurochemical and neuroanatomical patterns of degeneration that have been reported in PD patients with RBD compared to those without. The mechanisms and neural correlates that underlie the increased risk of apathy in PD patients with RBD require further investigation.

In addition, our data highlight an association and a considerable overlap between apathy and depressive symptoms, which is an expected finding considering the phenomenological overlap between both syndromes. However, in our cohort, a high number of patients, especially among subjects with RBD, had pure, isolated apathy. Similarly, more than half of the patients had an increased score in depression scale

but not in apathy scale. Our findings support the hypothesis, that these symptoms are dissociable also in patients with PD and apathy should not be considered as a mere symptom of depression [10].

The difference between the two groups in respect to apathy score are attributed mainly to the differences in the female group. In addition, we found an association between female gender and apathy, among the subjects in the PD-RBD+ group. Available data on gender differences among RBD patients are limited. Previous studies demonstrated no clear gender differences in respect to the frequency of RBD but reported significantly less behavior and less aggressive behavior during dreams in female PD patients with RBD compared to males [30,31]. It remains unclear whether the association between apathy and female gender is related to differences in the anatomy and physiology of limbic system dysfunction between males and females with PD [32], to gender-related activation patterns in limbic brain regions [33] or simply to differences in the course and therapy of PD. There is some evidence for an association between apathy and the female sex in the general population [34]. However, in our group of PD patients without RBD, the levels of apathy were comparable between male and female individuals. Further studies are needed to clarify this issue.

Previous studies showed that the presence of RBD in PD patients was associated with impaired performance in several cognitive domains and PD patients with RBD had a 3-fold higher risk of mild cognitive impairment (MCI) compared to patients without RBD [35]. In this cohort of PD patients, highly selected for absence of relevant cognitive deterioration and dementia (exclusion criterion for DBS surgery), we found, as expected, no differences in the cognitive score between PD-RBD+ and PD-RBD- patients. However, our report on cognitive impairment is based on the MMSE, which alone does not have adequate psychometric properties as a dementia screening instrument in PD patients [21].

In addition, the groups did not differ significantly in respect to PD staging, as measured by the H&Y scales, to motor disability, assessed by the UPDRS-III scale and to daytime sleepiness, assessed by the ESS. Finally, we found no significant differences for levodopa daily dosage, or antidepressant use between the two groups. These data highlight that the reported association between RBD and apathy, both isolated apathy or apathy in combination with depressive symptoms, occurs independent of stage of disease, degree of motor disability, other non-motor symptoms and medications.

5. Conclusion

The presence of RBD seems to increase the risk of apathy in PD patients. In addition, PD patients with RBD report more severe apathy symptoms than PD patients without RBD independent of age and years of PD. Similarly, PD patients with RBD report more often and more severe depressive symptoms compared to those without RBD. Therefore, this subgroup of PD patients with RBD should receive targeted medical attention to improve diagnosis, monitoring and management of neuropsychiatric symptoms and their consequences.

The mechanisms underlying the association between mood disturbances and RBD in PD remain speculative. RBD has been associated with lesions of the brainstem regions involved in muscle atonia and motor control during REM sleep and recent studies support the implication of brainstem regions in neuropsychiatric symptoms in PD. In addition, apathy and depression are strongly associated with the limbic system and there is increasing evidence on the involvement of limbic structures in the pathophysiology of RBD. Future studies should focus on the above brain structures in order to highlight the underlying pathophysiological mechanisms and neuroanatomical origin of apathy and depression in PD with RBD.

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Declarations of interest

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