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Sleep-Related Falling Out of Bed in Parkinson's Disease

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Background and Purpose Sleep-related falling out of bed (SFOB), with its potential for significant injury, has not been a strong focus of investigation in Parkinson's disease (PD) to date. We describe the demographic and clinical characteristics of PD patients with and without SFOB.

Methods We performed a retrospective analysis of 50 consecutive PD patients, who completed an REM sleep behavior disorder screening questionnaire (RBDSQ), questionnaires to assess for RBD clinical mimickers and questions about SFOB and resulting injuries. Determination of high risk for RBD was based on an RBDSQ score of 5 or greater.

Results Thirteen patients reported history of SFOB (26%). Visual hallucinations, sleep-related injury, quetiapine and amantadine use were more common in those patients reporting SFOB. Twenty-two patients (44%) fulfilled criteria for high risk for RBD, 12 of which (55%) reported SFOB. Five patients reported injuries related to SFOB. SFOB patients had higher RBDSQ scores than non-SFOB patients (8.2 ± 3.0 vs. 3.3 ± 2.0 , p<0.01). For every one unit increase in RBDSQ score, the likelihood of SFOB increased two-fold (OR 2.4, 95% CI 1.3-4.2, p<0.003).

Conclusions SFOB may be a clinical marker of RBD in PD and should prompt confirmatory polysomnography and pharmacologic treatment to avoid imminent injury. Larger prospective studies are needed to identify risk factors for initial and recurrent SFOB in PD.

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Key Words Parkinson's disease, REM sleep behavior disorder, sleep disturbance, falls, sleep-related injury.

Introduction

REM sleep behavior disorder (RBD) is characterized by loss of normal skeletal muscle atonia during REM sleep associated with vivid, and often, aggressive dreaming with patients performing dream-enacting behaviors.¹⁻³ These events are non-stereotypical and can range from simple, nonviolent motions (laughing, jerking) to more forceful, complex manifestations (yelling, punching, jumping from bed). RBD is a well recognized cause of sleep-related-injury in Parkinson's disease (PD).^{4,5} Sleep-related falling out of bed (SFOB) or "jumping out of bed" has been reported in studies of idiopathic RBD and sleep-related violence;^{1,2,6-9} but there is limited information about SFOB in PD.^{3-5,10,11} SFOB is not exclusively a symptom of RBD. It may occur during somnambulism, nocturnal seizures, violent periodic limb movements in sleep, or severe sleep disordered breathing (SDB).^{8,9,12}

RBD is a harbinger of neurodegenerative disease, with about 50% of patients eventually developing PD, multiple system atrophy, or Lewy body dementia approximately a decade from RBD onset.¹³ It can precede PD, occur simultaneously, or follow the diagnosis of PD.^{24,8,10,11,14} Prevalence estimates of RBD in the general and elderly population is low (0.4-0.5%),^{7,15} whereas in PD, it varies between 15-72%.^{4,5,10,14,16-20} Differing diagnostic criteria for PD and RBD, and selection bias may account for the observed variation in RBD rates in PD.

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To our knowledge, there is no study to date, describing SFOB in PD. Improved understanding of its prevalence in PD and predisposing patient characteristics may help improve rapid referral for comprehensive sleep medicine consultation and immediate institution of injury prevention strategies. In this study, we describe the demographic and clinical characteristics of PD patients with and without SFOB.

Methods

Subjects

We performed a retrospective analysis of 50 consecutive PD patients seen at the University of Miami Movement Disorders Clinic over a three month period (April-June 2009). PD diagnosis was made with clinical criteria according to UK Parkinson's Disease Society Brain Bank.²¹ Patients completed an assessment and examination by a movement disorders specialist, an RBD screening questionnaire (RBDSQ), questions about history of SFOB and SFOB-related injury and screening questions for SDB and somnambulism (both clinical mimickers of RBD). All patients had a minimum of two years of follow up prior to enrolling visit. Patients were excluded if they had a temporal association (within one month) of SFOB onset with the introduction of medications, particularly antidepressants. When possible, questionnaires were completed by the patient and bed partner. The study was approved by the University of Miami institutional review board. Informed consent was obtained from all patients participating in this study.



Fig. 1. Mean RBDSQ scores comparison. Data shown as mean \pm SD. *p*<0.01 for the comparison between the groups. RBDSQ: REM sleep behavior disorder screening questionnaire, SFOB: sleep-related falling out of bed.

Assessments

On the day of questionnaire completion, the following variables were collected: age, gender, PD duration, modified Hoehn and Yahr (H&Y) stage in the on-state, and medications. PD duration was calculated from the time the patient first reported PD motor symptoms. The levodopa equivalent daily dosage (LEDD) was calculated per published criteria.²² Medical records were reviewed for the following historical details: age of PD onset, history of dyskinesias, hallucinations, and mood/anxiety disorder. Mood or anxiety disorders were defined by medication use for these specific indications. The records were also reviewed for history of SFOB and related injuries mentioned during clinical visits.

RBDSQ

As developed by Stiasny-Kolster et al.²³ the RBDSO is a 10item, patient self-rating instrument reflecting the core clinical features of RBD as determined by the International Classification of Sleep Disorders-Revised Diagnostic and Coding Manual.²⁴ The features of the first nine items are listed in Fig. 1. Item 6 has four subparts (6.1-6.4) addressing motor and vocal phenomena associated with dreaming. Particularly pertinent to this study is item 6.3 with a question about SFOB within it: "I have or had the following phenomena during my dreams: gestures, complex movements that are useless during sleep (e.g. to wave, to salute, to frighten mosquitoes), falls off the bed (yes/no)".23 All PD patients scored positively on item 10 concerning presence of CNS disease and this item was excluded from Fig. 1. The maximum score of the RBDSQ is 13 points. It was originally validated in 54 PSGconfirmed RBD patients against control populations of sleep disorders patients and healthy sleepers.²³ Using a cut-off score of 5 as positive test for high risk for RBD, Stiasny-Kolster et al.23 reported a sensitivity of 96% and specificity of 56% when compared with patients with a variety of sleep disorders. Our PD patients were categorized as high risk for RBD if they scored ≥ 5 on the RBDSQ.

SFOB

History of SFOB and related injury were assessed with the following two questions: 1) "Have you ever fallen out of bed during sleep? If so, how many times have you fallen?" and 2) "Did you suffer any injuries from these falls? If so, what kind of injuries?"

RBD clinical mimickers

Screening questionnaires were used to detect for SDB and somnambulism, both of which have been associated with SFOB.^{8,9} The STOP questionnaire was utilized to identify high risk patients for SDB. This self-reported questionnaire asks four yes/ no questions about loud snoring, daytime tiredness, history of observed apneas, and history of hypertension or use of antihypertensive medication.²⁵ Patients were classified as high risk for SDB if they endorsed positive responses on at least two of four questions. This questionnaire has been validated in preoperative clinics with surgical patients with sensitivities for detecting mild, moderate, and severe obstructive sleep apnea of 65.6, 74.3, and 79.5%, respectively.²⁵ One question assessing adult-onset somnambulism was also included. A semi-structured telephone interview for parasomnia history was performed for those answering positively to this screening question. Participants reporting SFOB were asked to complete prolonged one hour electroencephalography (EEG) to objectively exclude underlying epileptic disorders. EEG was performed in accordance with the International 10-20 system.

Data analyses

Demographics and clinical characteristics, RBDSQ responses,

Table 1.	Demographic	and clinical	characteristics
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	All	SFOB	non-SFOB
	(n=50)	(n=13)	(n=37)
Demographics			
Age, years	68±12	65±9	69±12
PD onset, years	59±13	56±11	61±13
Sex (n, %)			
Male	34 (68)	10 (77)	24 (65)
Female	16 (32)	3 (23)	13 (35)
PD duration, years	9±4	10±5	8±4
Hoehn-Yahr stage	2.2±0.4	2.3±0.3	2.1±0.3
Education, years	15±3	14±4	15±3
Depression or anxiety	11 (22)	4 (31)	7 (19)
Visual hallucinations*	8 (16)	5 (38)	3 (8)
Dyskinesias	6 (12)	2 (15)	4 (11)
Sleep-related injury*	6 (12)	5 (38)	1 (3)
Medications			
LEDD (mg/day)	530±510	489±406	545±546
Levodopa/Carbidopa	37 (74)	12 (92)	25 (68)
Entacapone	7 (14)	1 (8)	6 (16)
Dopamine agonist	22 (44)	5 (38)	17 (46)
Amantadine*	16 (32)	8 (62)	8 (22)
MAO inhibitors	23 (46)	9 (69)	14 (38)
Antidepressants			
SSRIs	6 (12)	1 (8)	5 (14)
SNRIs	2 (4)	1 (8)	1 (3)
Bupropion	3 (6)	2 (15)	1 (3)
Quetiapine*	6 (12)	5 (38)	1 (3)
Cholinesterase inhibitors	6 (12)	3 (23)	3 (8)
Anticholinergics	14 (28)	4 (31)	10 (27)
Benzodiazepines	11 (22)	3 (23)	8 (22)

Data shown as means±SDs or frequency (%), as appropriate. *p<0.05.

LEDD: levodopa equivalent daily dosage, MAO: monoamine oxidase, PD: Parkinson's disease, SFOB: sleep-related falling out of bed, SSRI: selective serotonin reuptake inhibitor.

and RBD clinical mimickers questionnaire responses were compared for PD patients with and without SFOB.

Continuous variables are reported as means \pm (SD). The Mann-Whitney U test was used to compare nonparametric continuous and Chi-square or Fisher's exact test were used to compare categorical variables. A modified Bonferroni correction was applied for multiple comparisons concerning the individual RBDSO responses between the two groups.²⁶ Spearman's rank correlation test was utilized to assess correlations between the RBDSO total score and SFOB number, age of PD onset, age on questionnaire completion day, PD duration, H&Y stage and LEDD. Binary logistic regression analysis was performed to determine the clinical factors associated with prevalent SFOB. We entered all potential predictors of SFOB into a multiple logistic regression model without using backward or forward selection methods. We used the Hosmer-Lemeshow goodness-of-fit statistic (p>0.05) to evaluate model fit.

For all analyses, p < 0.05 was defined as statistically significant. Statistical analyses were performed with SPSS Statistics 17.0 (SPSS, Chicago, IL, USA).

Results

Demographics and clinical characteristics

The mean age of the 50 patients (34 men, 16 women) was 68.0 ± 11.6 years, and the mean age of PD onset was 59.4 ± 12.8 years with a duration of 8.5 ± 4.3 years and mean H&Y stage of 2.1 ± 0.3 . SFOB was present in 13 of the 50 patients. There were no significant differences between the SFOB and non-SFOB groups in gender distribution, mean age of PD onset, mean PD duration, mean H&Y stage, mean age at RBDSQ completion or mean education years (Table 1).

Visual hallucinations were more frequently reported in the SFOB group compared to the non-SFOB group. No differ-

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	All	SFOB	non-SFOB
	(n=50)	(n=13)	(n=37)
RBDSQ score*†	4.6±3.0	8.3±3.0	3.3±2.0
High risk RBD diagnosis (n, %)*	22 (44)	12 (92)	10 (27)
RBD clinical mimickers (n, %)			
High risk for SDB	16 (32)	4 (33)	12 (34)
Somnambulism	3 (6)	1 (8)	2 (6)
Questionnaires completed			
by (n, %)			
Patient alone	29 (58)	6 (46)	23 (62)
Patient and bed partner	21 (42)	7 (54)	14 (38)
*p<0.01, †RBDSQ reported as m	nean±SD.		

RBD: REM sleep behavior disorder, RBDSQ: REM sleep behavior disorder screening questionnaire, SDB: sleep disordered breathing, SFOB: sleep-related falling out of bed. ences between the groups were found regarding dyskinesias, depression or anxiety. None of the patients had a known history of seizure disorder.

Sleep-related injury was reported on the questionnaires and medical record review by 12% of patients and was more frequently reported in those with SFOB (Table 2). Overall, 13 patients reported a history of at least one SFOB (26%) on the questionnaire but only 8 had mentioned SFOB on their clinical visits; 5 (38%) patients reported only one episode, 3 patients (23%) reported two episodes and 5 (38%) patients reported more than two episodes of SFOB. The episodes were sometimes separated by months or years. Injuries in the clinical history and questionnaires included soft tissue trauma to neck, face, arms, and gluteus and one case of bitten tongue.

There was no significant difference between the SFOB and non-SFOB groups in their medications with the exception of higher use of amantadine and quetiapine in the SFOB group (Table 1). Two SFOB patients were prescribed amantadine for dyskinesias and six for anti-parkinsonian therapy. In the



Fig. 2. Individual RBDSQ item prevalence of SFOB (grey) and non-SFOB group (black). RBDSQ: REM sleep behavior disorder screening questionnaire, SFOB: sleep-related falling out of bed. *p<0.05, **p<0.01.

non-SFOB group, four patients used amantadine for dyskinesia and four more for anti-parkinsonian therapy. Of the 8 patients prescribed benzodiazepines, 5 (3 SFOB, 2 non-SFOB) were using clonazepam. All five SFOB patients with hallucinations were treated with quetiapine. None of the patients reported onset of SFOB within one month of introduction of antidepressant medication.

Questionnaires

The mean RBDSQ score was significantly higher in the SFOB group $(8.3\pm3.0 \text{ vs. } 3.3\pm2.0)$ (Fig. 1). Individual item response differences between the groups are shown in Fig. 2. The questionnaires were completed either by the patient alone (58%), or by the patient and bed partner (42%). Patients who completed the RBDSQ with their bed partner had a significantly higher score compared with those completing it alone (5.3 ± 2.6 vs. 4.0 ± 3.4 , p=0.033); however, there was no significant difference in bed partner participation in completion of questionnaires in either group (Table 2).

High risk for RBD categorization

Forty-four percent of patients fulfilled high risk for RBD criteria, 55% of whom reported SFOB (Table 2). Eight high risk for RBD patients (4 SFOB, 4 non-SFOB) were also high risk for SDB.

RBD clinical mimickers

There was no difference in the prevalence of patients who were at high risk for SDB or who reported somnambulism between the two groups. One high risk for RBD patient with SFOB reported multiple episodes of adult-onset somnambulism unrelated to medication use or snoring. Out of the non-SFOB patients with active history of somnambulism, one was high risk for OSA and the second patient's episodes were associated with zolpidem use. Three patients (1 SFOB, 2 non-SFOB) did not complete this questionnaire and were excluded from the statistical analysis.

Ten SFOB subjects (77%) completed one hour EEG, each including at least 10 minutes of sleep. Seven subjects had unremarkable EEG results, while the remaining 3 subjects had either intermittent left (1 subject) or right (2 subjects) temporal slowing. None of the subjects had finding suggestive of underlying seizure disorder (i.e. epileptiform activity or spike and wave pattern).

Correlation tests showed that the RBDSQ score is mildly associated with PD duration ($r_s=0.31$, p=0.025), H&Y stage ($r_s=0.37$, p=0.008) and LEDD ($r_s=0.32$, p=0.024) but not with SFOB number ($r_s=0.14$, p=0.32), age of PD onset ($r_s=-0.001$, p=0.99) or the age at RBDSQ completion ($r_s=0.081$, p=0.57).

Logistic regression analysis was performed to identify clin-

ical characteristics associated with SFOB in PD patients. Prevalent SFOB was the dependent variable and age, gender, PD duration, high risk for SDB, and RBDSQ score included as the independent variables. Goodness-of-fit testing revealed that the model accounted for the outcome better than chance alone (p<0.001) and that the predicted likelihood of the outcome was similar to the observed likelihood (p=0.24). The model performance was good with 67% of the variance in the outcome explained by the model. The overall accuracy of this model to predict subjects with prevalent SFOB (with a predicted probability of 0.5 or greater) is 94%. The sensitivity is 75% and the specificity is 100%. Positive predictive value is 100% and negative predictive value is 92%.

For every one unit increase in RBDSQ score the likelihood of SFOB increased by 2.4 (OR 2.4, 95% CI 1.3- 4.2, p<0.003). For every one unit increase in age, the likelihood of SFOB decreased by 6%. The latter, however, was not statistically significant. Similarly duration of PD, gender and risk for SDB did not have a statistically significant association with SFOB in our model.

Discussion

Prevalence of SFOB

This is the first study that focuses in detail on SFOB as a distinct clinical event in PD. SFOB was relatively common, reported by 26% of participants and significantly associated with sleep-related injury. Scaglione et al.⁴ found similar rates of "attempts to get out of bed," with 24% of PD patients with clinically-defined RBD reporting it occurred "sometimes"; however, it is unclear if these "attempts to get out of bed" are equivalent to SFOB. In a heterogenous sample, Lin et al.⁶ reported that 27% of Chinese patients with idiopathic and symptomatic PSG-verified RBD (including 11 with PD) had "accidental falling from the bed" In contrast, Iranzo et al.³ reported higher rates of falling out of bed (38.5%) in PD patients with PSG-verified RBD.

PD is predominantly a disease of older patients with its prevalence increasing with age.²⁷ Epidemiological studies estimate RBD prevalence to be 0.5% in older populations,¹⁵ while sleeprelated injury has been estimated to occur in 0.8% of the elderly.⁷ Falls in the elderly can have serious consequences including vertebral and hip fractures, head trauma or even fatal injuries.²⁸ Even minor injuries have the potential to further hamper mobility in PD patients. Overall, 12% of our PD patients reported sleep-related injury, approximately one-third of those with SFOB. This injury rate is consistent with that reported by Lin et al.⁶ (39%) who employed a retrospective design without bed partner involvement. Other investigations with higher rates of bed partner involvement have reported higher sleep-related injury rates associated with RBD in PD, recognizing that falling out of bed is a high risk event.^{4,5,10} The lower sleep-related injury rate reported may partially be explained by the injury assessment methods, limited to injuries resulting exclusively from sleep-related falls and not to other potentially dangerous manifestations of RBD (ie punching).

Patient characteristics

PD patients with SFOB were similar to those without SFOB in demographic, clinical characteristics and medication regimen except for the higher presence of visual hallucinations and the more common use of amantadine and quetiapine. In contrast to the older age, longer PD duration, higher H&Y stage, and male predominance noted in some of the larger studies of RBD in PD,4,14,20,29 we did not find these clinical variables were more common in patients reporting SFOB. Amantadine treatment was more common in the SFOB group compared to the non-SFOB group given its higher use as antiparkinsonian therapy. Visual hallucinations were more common in the SFOB group, explaining the higher use of quetiapine. The 5 patients with visual hallucinations were significantly older compared to the rest of the SFOB sample, and had multiple medical co-morbidities including depression, known risk factors for hallucinations in PD.30 It is possible that nocturnal hallucinations in the sleep-wake transition may have contributed to SFOB.

RBDSQ scores

Our study is one of the first to report on the range of RBDSQ scores in a PD population. Only two of the RBD patients in the original RBDSQ study had PD, and therefore, the usefulness of the RBDSQ in PD is currently unknown. Our patients with SFOB had significantly higher total mean RBDSQ scores than those without SFOB (Table 2). There was no difference in the distribution of patients with somnambulism or at high risk for SDB between the SFOB and non-SFOB groups, suggesting that overrepresentation of these clinical mimickers did not account for differences in RBDSQ scores.

We found a correlation between the RBDSQ score, PD duration, H&Y stage and LEDD. These three clinical variables represent markers of advanced PD. Longer PD duration and motor disability has been associated with RBD in PD, suggestive of more widespread brainstem pathology underlying REM sleep without atonia.^{4,10,29} The lack of correlation between RBDSQ score and SFOB number may be related to recall bias as most patients reported SFOB occurring in recent years. Although it has been shown to detect even mild manifestations of RBD, it is doubtful that the RBDSQ could be utilized to detect "severity" of RBD in PD as it does not include frequency of nocturnal behaviors. Li et al.³¹ recently-published a new RBD screening questionnaire (RBD-HK) which weighs lifetime occurrences of abnormal nocturnal behaviors and their frequency over the last year, providing a score for measuring RBD severity and tracking changes over time. Future studies should address the utility of these screening questionnaires to risk-stratify patients for initial or recurrent SFOB.

Our modeling was able to explain much of the variance in the dependent variable with good diagnostic performance. It highlights the importance of the RBDSQ score in predicting the odds of SFOB in patients with PD, with patients with higher scores (and thus increased probability of RBD) being more likely to fall out of bed.

High risk for **RBD** categorization and clinical mimickers

Overall, 44% of our participants screened high risk for RBD, a rate consistent with those reported in PD populations using clinical RBD criteria.^{4,10,14,29} SDB may have co-existed with RBD in 8 patients, a finding noted in the literature.^{10,11} In these patients, it is possible that RBD phenomena may have been triggered by REM sleep-related respiratory events. In our model, we did not find an association between increased risk for SDB and SFOB. Although three subjects had intermittent temporal slowing on extended one hour EEG, this finding has been noted in about 10% of elderly patients and is of unclear clinical significance.³² None of the SFOB patients completing 1 hour of EEG (10 patients) had definitive evidence suggestive of latent seizure disorder making the possibility that SFOB was an ictal phenomenon less likely.

Study limitations

Our study has several limitations, the most important of which is the absence of PSG to verify the clinical suspicion of RBD. A recent small case series from our group showed that in the majority of PD patients reporting SFOB (5 of 6), PSG confirmed suspected RBD diagnosis.33 The categorization of high risk for RBD was based on a discriminative score of 5 on the RBDSQ, a score which has not been validated in a PD population; however, other investigations have used this cut-off score in PD patients to determine RBD status.34 Unfortunatelv, we were unable to definitively diagnose RBD as many of the patients refused PSG due to cost or distance to our medical center. Since 2005, the International Classification of Sleep Disorders Coding and Diagnostic Manual 2nd edition requires PSG as part of RBD diagnostic criteria to exclude clinical mimickers of RBD and verify loss of normal skeletal muscle atonia during REM sleep.35 The prevalence of RBD in idiopathic PD assessed by clinical interviews alone varies between 15-46% and is increased to 46-58% when performed in conjuction with PSG.3 Hence, questionnaire assessment alone

is insufficient to diagnose RBD. Our high risk for RBD categorization is only suggestive and not diagnostic of RBD. We tried to objectively exclude nocturnal seizure phenomena by asking SFOB patients to complete daytime EEG. Unfortunately, all subjects could not undergo EEG due to absence of clinical indications. Although we tried to control for temporal association of medications known to influence RBD in the clinical history,^{36,37} it is possible that medications impacted SFOB occurrence or its absence; however, there was no significant differences in the use of these medication between the two groups. The majority of patients completed the questionnaires alone, likely underestimating the true prevalence of sleep-related complaints/RBD phenomena. Bed partner involvement will improve answers to some items on the RBDSQ as reflected by the significantly higher RBDSQ scores in those completing it with bed partners. Due to our small sample size, we could only control for a limited number of variables in our logistic regression analysis and we cannot exclude modest differences between groups.

The focus on SFOB is important as it is a potentially dangerous clinical but easily recognizable event. The natural history of SFOB in PD patients is currently unknown as are risk factors for future SFOB. Although we cannot equate SFOB with RBD in PD, when clinical events are highly suggestive of RBD, PSG confirms REM sleep without atonia in the large majority of cases. In our cohort, the majority of patients reporting fall-related injury had a history of SFOB before suffering injury, presenting a window of opportunity for intervention. Patients who may experience SFOB may not injure themselves and therefore, not report it to their healthcare provider. Asking about SFOB may be useful in busy movement disorders clinics to identify high-risk patients who merit expeditious sleep evaluation and immediate conservative treatment. Although patients reporting SFOB may represent only a fraction of PD patients with RBD, they may be a large proportion of those who require pharmacologic treatment to prevent imminent injury. Future prospective studies are needed to assess SFOB etiology in PD with PSG, define its natural evolution, risk factors for recurrent SFOB, and characterize its treatment response.

Conflicts of Interest .

The authors have no financial conflicts of interest.

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