Increased REM sleep without atonia in Parkinson disease with freezing of gait

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ABSTRACT

Objective: The objective of this cross-sectional study was to test the hypothesis that patients with Parkinson disease (PD) and freezing of gait (PD+FOG) would demonstrate sleep disturbances comparable to those seen in patients with REM sleep behavior disorder (RBD) and these changes would be significantly different from those in PD patients without FOG (PD-FOG) and age-matched controls.

Methods: We conducted overnight polysomnography studies in 4 groups of subjects: RBD, PD-FOG, PD+FOG, and controls. Tonic and phasic muscle activity during REM sleep were quantified using EMG recordings from the chin, compared among study groups, and correlated with disease metrics.

Results: There were no significant differences in measures of disease severity, duration, or dopaminergic medications between the PD+FOG and PD-FOG groups. Tonic muscle activity was increased significantly ($p < 0.007$) in the RBD and PD+FOG groups compared to the PD-FOG and control groups. There was no significant difference in tonic EMG between the PD+FOG and RBD group ($p = 0.364$), or in tonic or phasic EMG between the PD-FOG and control group ($p = 0.107$). Phasic muscle activity was significantly increased in the RBD group compared to all other groups ($p = 0.029$) and between the PD+FOG and control group ($p = 0.001$), but not between the PD+FOG and PD-FOG groups ($p = 0.059$).

Conclusions: These findings provide evidence that increased muscle activity during REM sleep is a comorbid feature of patients with PD who exhibit FOG as a motor manifestation of their disease.

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GLOSSARY

ESS = Epworth Sleepiness Scale; **FOG** = freezing of gait; **LED** = levodopa equivalent dose; **MMSE** = Mini-Mental State Examination; **NFOG-Q** = New Freezing of Gait Questionnaire; **PD** = Parkinson disease; **PPN** = pedunculopontine nucleus; **PSG** = polysomnography; **PSQI** = Pittsburgh Sleep Quality Index; **RBD** = REM sleep behavior disorder; **RSWA** = REM sleep without atonia; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Freezing of gait (FOG) is a major contributor to diminished quality of life and morbidity in Parkinson disease (PD).^{1,2} While disease progression remains the main risk factor for the development of FOG,³ not all patients develop FOG. Accordingly, the presence of FOG can be considered a subtype of PD with neuropathology that is separate from, but comorbid with, striatonigral dopaminergic degeneration.

The current consensus is that FOG emerges from changes in neuroanatomical networks in the brainstem, including the pedunculopontine nucleus (PPN) and locus ceruleus, that are components of the mesencephalic locomotor center and postural control circuits.⁴⁻⁶ Many of these anatomical regions have been implicated in the pathophysiology of REM sleep behavior disorder (RBD). RBD likely reflects a prodromal stage of PD that precedes the expression of cardinal motor symptoms.⁷ This idea is supported by evidence that increased muscle tone during REM sleep, REM sleep without atonia (RSWA), may be predictive of the future development of PD.^{8,9} While these observations point to RSWA as a potential marker of neurodegeneration, no

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studies have examined relationships between the degree of RSWA and the signs and symptoms of PD.

Several studies revealed associations between coexistent RBD, falls, and FOG in PD,^{10–12} suggesting that the co-occurrence of PD with FOG may be associated with worsening of RSWA compared to patients without FOG. The aim of this study was to compare muscle activity during REM sleep between patients with and without FOG, patients with RBD, and age-matched controls.

METHODS **Standard protocol approvals, registrations, and patient consents.** The study was approved by the institutional review board of Northwestern University. All subjects signed informed consent.

Subjects. This cross-sectional study enrolled 4 groups of subjects (10 subjects/group): 1) subjects with RBD; 2) subjects with PD with start hesitation and FOG (PD+FOG); 3) subjects with PD who did not have FOG (PD-FOG); and 4) age- and sex-matched controls. The inclusion criteria for the RBD group were a diagnosis of RBD based on the International Classification of Sleep Disorders II,¹³ age 45 to 75 years, and ability to ambulate independently without an assistive device. Subjects were excluded if they had another neurologic disorder, cognitive impairment (Mini-Mental State Examination [MMSE] score of <26), significant sleep apnea (defined as an apnea-hypopnea index >15 events/hour of sleep on polysomnography [PSG]), and significant periodic limb movement disorder (defined as a periodic limb movement index >10 events/hour of sleep with awakening on PSG). Subjects taking medications for RBD were allowed to participate as long as they remained on a stable dose for 2 months prior to the screening.

Subjects with PD were recruited based on the following criteria: a diagnosis of idiopathic PD based on the UK Parkinson's Disease Society Brain Bank criteria,¹⁴ Hoehn & Yahr stage 2 to 3, ability to ambulate independently without the use of an assistive device, age- (± 3 years) and sex-matched to the participants with RBD. The same exclusion criteria used for the RBD were used with the addition that patients with excessive tremor (a score >2 on item 20 of the Unified Parkinson's Disease Rating Scale [UPDRS]) and surgical treatments for PD were excluded. Subjects were assigned to PD+FOG if they had a history of start hesitation and freezing episodes, based upon the New Freezing of Gait Questionnaire (NFOG-Q),^{15,16} and had at least one weekly FOG episode (a score of >1 on item 3 of the NFOG-Q). Subjects in the PD-FOG and PD+FOG groups were matched for levodopa equivalent dose (LED $\pm 20\%$). The subjects with PD were recruited for the study on the basis of the presence or not of FOG prior to their sleep assessment. Control subjects were age- and sex-matched to participants with RBD. Exclusion criteria for the control subjects were the same as in the RBD group.

All subjects underwent a clinical evaluation including a comprehensive neurologic examination, the UPDRS, and completed the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI).

Sleep assessment. All subjects underwent a PSG in the Sleep Laboratory at Northwestern Memorial Hospital. The recording montage included right/left electro-oculograms, submental and right/left tibialis anterior EMG, EEG, nasal and oral airflow,

thoracic and abdominal respiratory effort, and oxygen saturation. PSGs were scored by a physician certified in sleep medicine who remained blinded to subject data.

Sleep stages were scored according to the American Academy of Sleep Medicine Manual for Scoring Sleep.¹³ Tonic and phasic muscle activity were quantified during REM sleep using the submental (chin) EMG signal.¹⁷ The tonic muscle activity was defined as the presence of increased EMG activity during REM sleep exceeding twice the background activity in stage N3 sleep. Each 30-second epoch was scored as tonic or atonic depending on whether tonic chin EMG activity was present for $\geq 50\%$ or $< 50\%$ of the epoch. The percentage of REM sleep with tonic muscle activity (% tonic EMG) was derived from the sum of all epochs containing increased tonic muscle activity divided by the REM sleep time. The phasic muscle activity was assessed in 3-second mini-epochs during REM sleep. A phasic EMG event was defined as any burst of EMG activity lasting 0.1 to 5 seconds with amplitude exceeding 4 times the background EMG activity. The percentage REM sleep with phasic muscle activity (% phasic EMG) was derived from the sum of all mini-epochs containing increased muscle phasic activity divided by the REM sleep time. In addition to the 2 primary dependent variables (% phasic EMG, % tonic EMG), the following variables were also quantified: total sleep time, sleep efficiency, sleep latency, REM latency, and % of N1, N2, N3, and REM sleep.

Statistical analysis. Dependent variables that fulfilled the assumption of a normal distribution, based on a Shapiro-Wilk test, were analyzed using a univariate analysis of variance in SPSS (version 20). Significant main effects of group were further examined by post hoc tests between groups using Tukey honestly significant difference test. The nonparametric Kruskal-Wallis test was used to examine differences between groups for data with a non-Gaussian distribution (% tonic EMG, % phasic EMG, sleep efficiency, sleep latency, REM latency, N1, N2, N3 sleep, and Hoehn & Yahr stage). Estimates of the effect size are reported using the η^2 value. The p values less than 0.05 were considered significant.

RESULTS **Demographics and clinical assessment.** A summary of the subject demographics, medications, and clinical evaluations is provided in table 1. There were no differences between groups in age or MMSE scores. The PD+FOG group tended to have a longer disease duration, higher dose of parkinsonian medications, and increased total UPDRS and UPDRS III scores compared to the PD-FOG group, but these differences did not reach significance ($p > 0.052$). Hoehn & Yahr ratings were significantly higher in the PD+FOG compared to the PD-FOG group ($p = 0.045$). Several of the RBD subjects were taking clonazepam ($n = 5$; dose range 0.5–2 mg) and melatonin ($n = 3$; dose range 3–15 mg). None of the RBD subjects was taking an antidepressant. A few of the subjects in the PD-FOG group were taking clonazepam ($n = 1$; 1 mg), melatonin ($n = 1$; 3 mg), or paroxetine ($n = 1$; 20 mg). Similarly, several of the subjects in the PD+FOG group were taking clonazepam ($n = 3$; dose range 0.5–1 mg) or escitalopram ($n = 3$; dose range 5–15 mg). One subject in the PD-FOG group and 3 subjects in the PD+FOG group had an established diagnosis of RBD. Two

Table 1 Demographics and disease characteristics of the study participants

	Controls (n = 10)	PD-FOG (n = 10)	PD+FOG (n = 10)	RBD (n = 10)	Statistics (p value ^a)
Age, y	62.7 ± 11.5	61.5 ± 9.4	65.9 ± 11.2	61.5 ± 8.6	0.747
Sex, M/F	8/2	8/2	8/2	6/4	
Age at diagnosis, y	NA	57.3 ± 9.1	59 ± 9.4	58.5 ± 9.3	0.695 ^b
Duration of symptoms, y	NA	4.4 ± 2.5	7.2 ± 4.1	1.3 ± 0.9	0.090 ^b
Hoehn & Yahr stage	NA	2.0 ± 0.2	2.2 ± 0.3	NA	0.045 ^b
UPDRS I-IV	1 ± 1.7	28.1 ± 19.6	40.9 ± 20.7	2.5 ± 3.7	0.053 ^b
UPDRS III	0.9 ± 1.4	18 ± 6.3	25.6 ± 10.5	1.5 ± 1.9	0.066 ^b
LED, mg	0	582 ± 436	727 ± 254	0	0.356 ^b
Schwab and England	NA	89 ± 3	88 ± 4	NA	0.556 ^b
MMSE	30 ± 0	30 ± 1	30 ± 1	30 ± 0	0.382
NFOG-Q	0	0	17 ± 5	0	<0.001 ^b
Medications, n					
Antidepressants	0	1	3	0	
Melatonin	0	1	0	3	
Clonazepam	0	1	3	5	

Abbreviations: LED = levodopa equivalent dose; MMSE = Mini-Mental State Examination; NA = not applicable; NFOG-Q = New Freezing of Gait Questionnaire; PD+FOG = Parkinson disease patients with freezing of gait; PD-FOG = Parkinson disease patients without freezing of gait; RBD = REM sleep behavior disorder; UPDRS = Unified Parkinson's Disease Rating Scale.

^aThe p value reported is for the test of the main effect of group.

^bDenotes p value for comparison between PD-FOG and PD+FOG.

subjects in the PD-FOG group and one subject in the PD+FOG group reported vivid dreams associated with vocalizations and movements, but did not meet diagnostic criteria for RBD.

Sleep assessment. Table 2 provides a summary of sleep measures. Excessive daytime somnolence, as defined by ESS score ≥10, was not present in any of the study groups. The subjects in the PD+FOG group had poor sleep quality, as assessed by total PSQI score >5, but there were no differences in this measure

across groups. There were no main effects of group in most of the PSG measures, including total sleep time, sleep efficiency, sleep latency, REM sleep latency, and the percentage of sleep across sleep stages (N1, N2, N3, REM).

The main finding from this study was a marked increase in the percentage of both tonic and phasic EMG activity during REM sleep in both the RBD and PD+FOG groups compared to the PD-FOG and control groups (figure). In particular, there was a large increase in tonic EMG in the PD+FOG

Table 2 Sleep measures and polysomnographic parameters of the study participants

	Controls (n = 0)	PD-FOG (n = 10)	PD+FOG (n = 10)	RBD (n = 10)	Statistics (p value ^a)
ESS	5.4 ± 3.6	8.9 ± 3.9	7.8 ± 3.7	7.6 ± 6.8	0.276
PSQI	3.6 ± 2.1	5.2 ± 2.7	7.5 ± 5.6	5.4 ± 3.8	0.235
Total sleep time, min	323.7 ± 45.3	337.1 ± 39.1	332.5 ± 54.9	358.9 ± 79.9	0.334
Sleep efficiency, %	82.3 ± 10.2	84.9 ± 6.4	79.8 ± 9.6	84.2 ± 15.3	0.341
Sleep latency, min	13 ± 18.5	4.7 ± 5.4	8.3 ± 7.9	7.9 ± 9.0	0.676
REM latency, min	97.5 ± 60.4	118.6 ± 65.6	82.8 ± 67.7	141.1 ± 74.9	0.203
N1 sleep, %	9.7 ± 4.9	13.4 ± 5.6	16.4 ± 7.9	11.1 ± 9.1	0.089
N2 sleep, %	59.1 ± 11.7	60.4 ± 12.9	55.3 ± 15.3	64.2 ± 12.2	0.444
N3 sleep, %	13.8 ± 11.0	6.7 ± 6.7	5.0 ± 8.2	5.3 ± 5.2	0.111
REM sleep, %	17.3 ± 7.5	19.6 ± 9.1	20.1 ± 12.4	19.4 ± 8.5	0.960

Abbreviations: ESS = Epworth Sleepiness Scale; PD+FOG = Parkinson disease patients with freezing of gait; PD-FOG = Parkinson disease patients without freezing of gait; PSQI = Pittsburgh Sleep Quality Index; RBD = REM sleep behavior disorder.

^aThe p value reported is for the test of the main effect of group.

Figure Tonic and phasic EMG activity in REM sleep

Box and whisker plots of the percentage of REM sleep with (A) tonic EMG activity or (B) phasic EMG activity. The lower and upper limits of the boxes delineate the 25th and 75th percentiles of the data, the whiskers show the 5th and 95th percentiles, the horizontal line shows the median, and the open square shows the mean within the group. Note the considerable overlap of the distribution of tonic EMG activity in the Parkinson disease (PD) and freezing of gait (PD+FOG) and REM sleep behavior disorder (RBD) groups. PD-FOG = PD patients without FOG.

group as shown by an 8-fold and 3-fold increase in activity compared to the control and PD-FOG groups, respectively. A main effect of group was obtained for tonic EMG ($\chi^2 = 23.19$, $df = 3$, $p < 0.001$, $\eta^2 = 0.59$) and phasic EMG ($\chi^2 = 22.71$, $df = 3$, $p < 0.001$, $\eta^2 = 0.58$). Post hoc tests showed that tonic EMG was increased in both the RBD and PD+FOG groups compared to the control and PD-FOG groups ($\chi^2 > 7.41$, $p < 0.007$, $\eta^2 > 0.38$). There were no tonic EMG differences between the RBD and PD+FOG groups ($\chi^2 = 0.82$, $p = 0.364$) or between the PD-FOG and control groups ($\chi^2 = 2.588$, $p = 0.108$). Phasic EMG was increased in both the RBD and PD+FOG groups compared to the control group ($\chi^2 > 11.57$, $p < 0.002$, $\eta^2 > 0.38$) and between the RBD group and both the PD+FOG and PD-FOG groups ($\chi^2 > 4.79$, $p < 0.020$, $\eta^2 > 0.25$), but the difference between the PD+FOG and PD-FOG groups did not reach significance ($\chi^2 = 3.58$, $p = 0.059$).

DISCUSSION The first main finding from this study was the marked difference in tonic muscle activity during REM sleep between PD subjects with and without FOG. It is important to reiterate that these groups were recruited on the basis of the presence or absence of a history of start hesitation and freezing and not sleep behavior. Both cohorts were matched by age and sex, and although the PD+FOG group tended to have a longer disease duration and higher LED and total UPDRS scores, these differences did not reach significance. The difference in tonic RSWA between the PD+FOG and PD-FOG group was large even after removing subjects with a diagnosis of RBD from the analysis, demonstrating that RSWA

differentiated these groups even in the absence of dream enactment. On average, the percentage of tonic EMG activity was threefold higher in the PD+FOG group compared to the PD-FOG group (30% vs 10%). Measures of phasic EMG activity were elevated in PD+FOG compared to PD-FOG but did not reach the level of significance ($p = 0.059$). The absence of a significant group difference for measures of phasic EMG activity is consistent with a study showing that patients with RBD who developed PD showed significant changes in tonic EMG, but not phasic EMG, compared to patients who remained disease-free.⁹

Previous investigations have focused on relationships between clinical features and the coexistence of either RBD or other features of sleep. Patients with PD with coexistent RBD are more likely to manifest a nontremor PD subtype.^{10,11,18} Similarly, higher phasic EMG activity during REM sleep was found in patients with PD with symmetric disease and akinetic-rigid subtype compared to tremor-predominant patients.¹⁹ A similar comparison could not be conducted in our study since tremor-predominant patients were specifically excluded (due to criteria related to a larger study²⁰). This exclusion criterion may have biased our sample toward subjects with RSWA. Nonetheless, this bias was the same for both the PD-FOG and PD+FOG groups. Thus, our findings expand upon previously reported findings by showing that abnormal muscle activity during REM sleep is most marked in subjects with FOG and this association is likely much stronger than the presence of an akinetic-rigid syndrome alone.

Several cross-sectional studies have investigated associations between the coexistence of RBD and

postural instability and gait dysfunction in patients with PD, yet the findings have been discordant. Three studies have reported an increased frequency of falls in patients with PD and RBD compared to patients without RBD.^{10–12} In a study of 36 patients with PD, the frequency of falls was significantly higher (5.4 times) in patients with PD and RBD compared to patients without RBD.¹⁰ That study also showed a more than threefold increase in the frequency of freezing episodes in the PD with RBD group. This finding was recently replicated in a larger sample of patients.¹¹ Considering that the presence of FOG is associated with a higher risk of falls,^{21,22} our findings appear to be consistent with these results. Yet a recent study that used static and dynamic posturography and gait analysis to compare postural stability and gait dysfunction between PD patients with and without RBD failed to find differences between groups.²³ These results do not directly refute previously reported findings since static and dynamic posturography measures are poor predictors of future falls.^{24,25} In addition, this study did not report the number of patients with FOG and did not examine phasic or tonic EMG activity during REM sleep, so it is difficult to directly compare their findings to the results of the present study. Nonetheless, the absence of differences in postural control and gait between PD patients with and without RBD raises the possibility that the commonalities in REM sleep dysfunction between the RBD and PD+FOG groups in the present study may reflect an overlap in the circuits that control muscle activity during REM sleep and FOG, but not postural stability.

Our second main finding was the similarity in the amount of tonic EMG activity during REM sleep in PD+FOG and RBD groups. It has been proposed that RSWA in PD evolves from alterations in descending input from the substantia nigra that override inhibitory signals of REM sleep, likely at the level of mesopontine areas, primarily the PPN and mid-brain extrapyramidal area, as well as locus ceruleus/subceruleus and magnocellular reticular formation.¹⁹ Yet, despite evidence of nigrostriatal dopaminergic dysfunction in RBD,²⁶ the amount of EMG activity during REM sleep does not correlate with striatal dopamine terminal density.²⁷ The basal ganglia contributions to REM sleep dysfunction may be secondary to a primary degeneration in the PPN and other brainstem nuclei implicated in RSWA.^{26,28} Cholinergic denervation or dysfunction, likely caused by the loss of cholinergic neurons of the PPN, has also been shown in patients with PD who are fallers²⁹ or have coexistent RBD,²⁸ and has been implicated as a factor contributing to gait disturbance in PD.³⁰ These data are consistent with the idea that nondopaminergic systems contribute to both RSWA and FOG in

patients with PD. This would also be consistent with the resistance of FOG symptoms to treatment with dopaminergic drugs, particularly late in disease progression, when FOG often becomes a major debilitating feature of the disease. Similarly, the symptoms of RBD are largely resistant to treatment with dopaminergic drugs.

The data presented in this study demonstrate a relationship between RSWA and PD with FOG and that the disturbance in REM sleep muscle activity is similar to that seen in patients with RBD. Previous studies have shown that the severity of tonic RSWA in RBD is predictive of the development of PD.⁹ Our findings extend and refine this hypothesis by suggesting that the presence of excessive tonic EMG activity during REM sleep may be predictive of development of a subtype of PD that is dominated by FOG. Moreover, these findings provide evidence suggesting that the pathophysiologic mechanisms that mediate FOG in PD share a common subset of neurodegenerative changes that mediate RSWA in RBD. Longitudinal studies including larger cohorts of subjects are needed to examine the evolution of changes in muscle activity during REM sleep in the RBD and PD populations, and its possible relevance as a predictor of FOG and gait impairments in PD.

AUTHOR CONTRIBUTIONS

Dr. Videnovic: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. C. Marlin: acquisition of data, critical revision of the manuscript for important intellectual content, study supervision. Dr. Alibiglou: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Planetta: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Vaillancourt: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. MacKinnon: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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