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Probable RBD is Increased in Parkinson's Disease But Not in Essential Tremor or Restless Legs Syndrome

Charles H. Adler, MD, PhD[a,*], **Joseph G. Hentz, MS**[b], **Holly A. Shill, MD**[c], **Marwan N. Sabbagh, MD**[c], **Erika Driver-Dunckley, MD**[a], **Virgilio G.H. Evidente, MD**[a], **Sandra A. Jacobson, MD**[c], **Thomas G. Beach, MD, PhD**[c], **Bradley Boeve**[d], and **John N. Caviness, MD**[a]

[a] Department of Neurology, Mayo Clinic, Scottsdale, AZ

[b] Department of Biostatistics, Mayo Clinic, Scottsdale, AZ

[c] Banner Sun Health Research Institute, Sun City, AZ

[d] Department of Neurology, Mayo Clinic, Rochester, MN

Abstract

Objective—Compare the frequency of REM sleep behavior disorder (RBD) and excessive daytime sleepiness (EDS) in Parkinson's disease (PD), restless legs syndrome (RLS), essential tremor (ET), and control subjects.

Methods—Subjects enrolled in a longitudinal clinicopathologic study, and when available an informant, completed the Mayo Sleep Questionnaire, which asks "Have you ever been told that you act out your dreams?", and the Epworth Sleepiness Scale (ESS).

Results—Probable RBD (based on informant response to the questionnaire) was much more frequent in PD (34/49, 69%, $p<0.001$) than in RLS (6/30, 20%), ET (7/53, 13%), or control subjects (23/175, 13%), with an odds ratio of 11 for PD compared to controls. The mean ESS and the number of subjects with an ESS ≥ 10 was higher in PD (29/60, 48%, $p<0.001$) and RLS (12/39, 31%, $p<0.001$) compared with ET (12/93, 13%) and Controls (34/296, 11%).

Conclusions—Probable RBD is much more frequent in PD with no evidence to suggest an increase in either RLS or ET. Given the evidence that RBD is a synucleinopathy, the lack of an increased frequency of RBD in subjects with ET or RLS suggests the majority of ET and RLS subjects are unlikely to be at increased risk for developing PD.

Keywords

Parkinson's disease; REM sleep behavior disorder; essential tremor; restless legs syndrome; excessive daytime sleepiness

[*]Correspondence: Charles H. Adler, MD, PhD, Professor of Neurology, Mayo Clinic Arizona, 13400 E. Shea Boulevard, Scottsdale, AZ 85259 Phone: 480-301-6328 Fax: 480-301-8451 cadler@mayo.edu.

Introduction

In the past decade the field of sleep abnormalities in movement disorder patients has exploded. Numerous studies have found an association between REM sleep behavior disorder (RBD) and synucleinopathies, Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy. Data suggests that RBD is a pre-motor finding for PD.[1–5] Estimates for the prevalence of RBD being 0.5% in the general population come from a single study[6] while it is estimated that up to 60% of PD subjects have RBD.[2, 7] On the other hand, in subjects diagnosed with idiopathic RBD it is estimated that ~40–65% go on to develop PD or DLB.[1, 8, 9]

There are no studies published investigating RBD in either essential tremor (ET) or restless legs syndrome (RLS). As some hypothesize that ET is related to PD and Lewy bodies,[10] it might be expected that RBD would be more common in patients with ET. Similarly, while any relationship between RLS and PD has been limited at best, if there is a causal relationship between RLS and PD then given the prevalence of RLS, RBD might be expected to occur more frequently in RLS subjects than the general population.

Utilizing clinical data and the Mayo Sleep Questionnaire from subjects enrolled in a longitudinal clinicopathological study, the current analysis assessed the frequency of probable RBD and excessive daytime sleepiness in PD, RLS, ET, and similarly assessed control subjects.

Methods

All subjects were enrolled in an ongoing longitudinal clinicopathological study, the Banner Sun Health Research Institute Brain and Body Donation Program,[11] and all signed written informed consent approved by the Institutional Review Board. Subjects were volunteers from the community who signed up for eventual brain and body donation with some of the PD cases having been recruited from the investigators' clinical practices. All subjects received a standardized movement disorders examination as previously described.[12] Subjects, and when available an informant, completed the Mayo Sleep Questionnaire (MSQ) [13, 14] and the Epworth Sleepiness Scale (ESS).[15]

Following each evaluation subjects received a movement disorder diagnosis including 1) Clinically probable PD (PD) defined as 2 of the 3 cardinal signs (rest tremor, bradykinesia, cogwheel rigidity), no symptomatic cause, and a response to dopaminergic medications,(9) 2) RLS based upon published criteria,[16] 3) ET based on an examination finding of grade ≥2 tremor of the limbs, or ≥1 tremor persisting over 3 years of longitudinal assessments, or isolated head tremor (without dystonia), or a previous diagnosis of ET and a clinical assessment consistent with the diagnosis, and without identifiable secondary cause or other exclusion criteria (eg. drug-induced tremor, prominent unilateral tremor, rigidity, or bradykinesia),[17] and 4) Control group (subjects were excluded if they had evidence of any other form of parkinsonism or dementia). Of 561 eligible subjects, 519 had a single diagnosis of interest (PD, ET, or RLS) while 42 subjects had more than one diagnosis of interest and were therefore excluded from the analysis.

Each sleep questionnaire was linked to the closest movement diagnosis within 1 year and we selected each subject's most recent sleep questionnaire results. Comparisons of mean scores were made by using the two-sample *t* test, and adjusted means were compared by using a general linear model. Comparisons of binomial measures were made by using the Pearson chi-square test, and adjusted comparisons were made by using multiple logistic regression. Boeve et al. have previously shown that screening positive for question 1 "Have you even been told that you act out your dreams?" on the informant completed version of the MSQ

has >98% sensitivity and ≥74% specificity for polysomnogram confirmed RBD,[13] so this study used the informant data from question 1 as a marker of RBD, with those screening positive being labeled as “probable RBD” (pRBD) for purposes of this analysis.

Results

We identified 307 subjects: 49 PD, 30 RLS, 53 ET, and 175 Control (Table 1) who had informant data for the question “Have you even been told that you act out your dreams?” Demographic data is in table 1 showing the differences in mean age and gender distribution between groups. The number of cases excluded was: 7 PD+RLS, 4 PD+ET, 12 RLS+ET, and 1 PD+RLS+ET.

Probable REM sleep behavior disorder based on informant responses to question 1 showed a higher frequency in PD (69%) than in controls (13%) (table 1). The odds ratio for pRBD in PD, after correction for age and gender, was 11 (table 1). The frequency of pRBD did not differ between RLS and controls or ET and controls (table 1). While pRBD in control subjects was more frequent in men (14/79 18%) than women (9/96 9%), this was not statistically significant.

The analysis of ESS data utilized participant and not informant responses. Therefore, the number of subjects who completed the ESS was greater. There were 488 subjects total: 60 PD, 39 RLS, 93 ET, and 296 controls. The number of cases excluded was: 12 PD+RLS, 5 PD+ET, 21 RLS+ET, 2 PD+RLS+ET. Using the mean ESS scores, excessive daytime sleepiness was more frequent in both the PD (10.2 ± 5.6) and RLS (6.9 ± 5.6) groups compared with controls (5.2 ± 3.7), with no difference found in the ET (5.6 ± 3.7) group (table 2). Using a cut-off score of ≥10 for the ESS as being “clinically significant”, 48% of the PD and 31% of the RLS were above this level compared with 13% of the ET and 11% of the Controls.

Discussion

Our findings demonstrate that the frequency of probable REM sleep behavior disorder was much greater in people with Parkinson’s disease than those with restless legs syndrome, essential tremor, and controls. There is now substantial data establishing RBD as a synucleinopathy and pre-motor finding in PD, dementia with Lewy bodies, and multiple system atrophy.[2–4, 9, 18] RBD is usually diagnosed by polysomnography, but recently, Boeve et al.[13] have shown that with the Mayo Sleep Questionnaire pRBD can reliably be diagnosed without the sleep study. As polysomnography is time consuming and expensive, a screening questionnaire allows for investigating pRBD in larger populations.

The BSHRI cohort is predominantly volunteers from the community enrolled with the intent of donating their brains and bodies for research purposes. While patients with PD are recruited in some cases, there is no recruitment of ET or RLS cases. All subjects receive extensive annual assessments and the sleep questionnaire was added to this assessment in 2006. The findings in this study are unique as all subjects (PD, ET, RLS, and controls) were similarly assessed and there are no previous systematic studies of RLS or ET nor previous data comparing subjects with PD and controls. Given the evidence that RBD is a synucleinopathy it was of great interest to determine whether RBD is more common in ET or RLS.

Some have hypothesized that ET is a risk factor for PD and that there may be a “Lewy body variant” of ET[19] although follow-up data was less suggestive of this hypothesis.[20] This hypothesis has not been supported by our own work which did not find an increase in Lewy bodies in ET,[17] nor did we find an increase in ET prevalence in a series of incidental

Lewy body disease cases when compared to controls.[21] A more detailed review of this lack of an association between ET and PD was recently published.[22] If ET was a variant of PD, or a risk factor for developing PD, given the prevalence of ET we would have expected some increase in the occurrence of RBD in the ET group, and this was not found.

The coexistence of RLS in PD patients has been reported although whether RLS is more frequent in PD remains unclear.[23–27] No data is available to show that RLS patients are at increased risk for developing PD and nor that RLS is a synucleinopathy. Our data showing that pRBD was not increased in RLS cases suggests it is unlikely to be pre-motor PD.

Excessive daytime sleepiness in PD has been well documented.[28, 29] Our data showing a higher overall mean for the Epworth Sleepiness Scale, and a higher percentage of cases having an abnormal score (≥10) than controls is thus confirmatory. The finding that subjects with RLS had a higher mean score and a higher percentage of cases with a score ≥10, confirms results from other recent studies.[30] While the mean score was only minimally, but significantly elevated, the percentage of cases with a score ≥10 suggests a correlation. No evidence was found for EDS in ET, and to date there are no published reports of this.

One limitation to this study is sample size although the difference in the frequency in pRBD in PD is extremely large suggesting a clear difference between groups. A second limitation is our inability to determine whether medications may have impacted MSQ or ESS scores given the original design of the database (medications were not systematically recorded at the time the questionnaire was completed). While the use of the MSQ with a single question for RBD was used, the data presented was all from informant responses and this has previously been shown to have 98% sensitivity for RBD when validated with a sleep study.[13] A further limitation is the paucity of longitudinal follow-up data on the subjects to determine whether ET or RLS cases with RBD are at increased risk of developing PD. As all cases are enrolled in our brain and body donation program longitudinal data is being collected and may eventually be enough for analysis. Additionally, as the number of cases with ET plus RLS is small, the possibility that subjects with both these disorders may be at increased risk for PD cannot be determined.

The lack of an association between pRBD and either ET or RLS suggests that the majority of patients with ET or RLS likely do not have a synucleinopathy. Larger numbers of cases, further longitudinal assessments, and neuropathologic examination of these cases will eventually further increase the accuracy of these results.

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Table 1

Demographics and results for the Mayo Clinic Sleep Questionnaire Question 1 as completed by an informant.

	PD	RLS	ET	Control
N	49	30	53	175
Female	19 (39%)	23 (77%)	15 (28%)	96 (55%)
Age (y); mean (SD)	72.8 (8.6)	76.0 (7.4)	81.4 (6.5)	79.4 (7.3)
Question 1 (yes vs. no)				
# Yes (%)	34 (69%)	6 (20%)	7 (13%)	23 (13%)
95% CI	0.42 to 0.70	−0.08 to 0.22	−0.10 to 0.10	Reference
P	<.001	.32	.99	Reference
Adjusting for Gender and Age				
Odds Ratio	11	1.82	1.03	Reference
95% CI	5.1 to 24	0.63 to 5.2	0.40 to 2.7	Reference
P	<.001	.26	.95	Reference

Table 2

Demographics and results for Epworth Sleepiness Scale as completed by the subject.

	PD	RLS	ET	None
N	60	39	93	296
Female	26 (43%)	33 (85%)	45 (49%)	201 (68%)
Age (y); mean (SD)	73.8 (9.4)	76.8 (7.9)	82.9 (6.7)	80.2 (7.8)
ESS				
Mean (SD)	10.2 (5.6)	6.9 (4.7)	5.6 (3.7)	5.2 (3.7)
95% CI	3.9 to 6.1	0.5 to 3.1	−0.4 to 1.3	Reference
P	<.001	.006	.28	Reference
Adjusting for Gender/Age; mean	9.9	7.3	5.6	5.4
95% CI	3.4 to 5.7	0.7 to 3.2	−0.6 to 1.1	Reference
P	<.001	.003	.58	Reference
Cases with ESS ≥10	29 (48%)	12 (31%)	12 (13%)	34 (11%)
95% CI	0.24 to 0.50	0.04 to 0.34	−0.06 to 0.09	Reference
P	<.001	.001	.71	Reference