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Longitudinal changes in cognition in early Parkinson's disease patients with REM sleep behavior disorder

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Abstract

Introduction—Cognitive decline is common in Parkinson's disease (PD), and identifying patients at highest risk for it is essential. We aimed to examine the effect of possible REM sleep behavior disorder (pRBD) on rate of cognitive decline in early PD, for both global cognition and in specific cognitive domains.

Methods—Parkinson's Progression Markers Initiative (PPMI) is a multi-site, international study of PD patients untreated at enrollment. pRBD was assessed with the REM sleep behavior disorder questionnaire (RBDSQ). Global cognition was assessed at baseline and annually using the Montreal Cognitive Assessment (MoCA) and a cognitive battery. Linear mixed effects models were used to examine the relationship between pRBD (RBDSQ ≥ 6) and rate of change in cognitive variables. Age, sex, years of education, and baseline motor and cognitive scores were included as covariates.

Results—The baseline sample consisted of 423 individuals with PD, mean age 61.7 years and 65.5% male. Data was available on 389, 366, and 196 participants at 1-year, 2-year, and 3-year follow-up respectively. Possible RBD occurred in 108 (25.5%) at baseline. In multivariate analyses, baseline RBD was associated with greater annual rate of decline in MoCA score ($\beta = -0.34$, 95%CI $-0.54, -0.13$, $p < 0.001$), Symbol Digit Modalities Test ($\beta = -0.69$, 95%CI -1.3 ,

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Conflicts of interest

None of the authors have potential conflicts of interest that relate to the research covered in the article.

−0.09, $p = 0.024$), and Hopkins Verbal Learning Test-Revised, delayed free recall ($\beta = -0.21$, 95% CI −0.41, −0.013, $p = 0.037$).

Conclusions—Possible RBD is common in early PD and predicts future cognitive decline, particularly in attention and memory domains.

Keywords

REM sleep behavior disorder; Cognition; Dementia

1. Introduction

In Parkinson's disease (PD), cognitive impairment and dementia occur in as many as 80% of patients long-term [1], and are associated with poor outcomes [2]. Understanding of predictors of PD cognitive decline remains limited, and effective therapies are needed. Given the significance of cognitive dysfunction in PD, identifying factors that contribute to it, such as sleep abnormalities, is essential. Rapid eye movement sleep behavior disorder (RBD) is one of the most common sleep disorders in PD, occurring in about half of patients [3]. Multiple studies have confirmed that RBD is a risk factor for cognitive dysfunction and decline in advanced PD [4–6]. Few studies have investigated this in early PD, when interventions to prevent cognitive decline could potentially have the greatest impact [7]. An association between dream enactment behavior, as occurs in RBD, and global cognitive decline has been reported in a preliminary analysis of a subset of early, untreated PD patients enrolled in the Parkinson's Progression Markers Initiative (PPMI) cohort [8]. The objectives of this study were to (i) confirm the association between possible RBD and cognitive decline in early PD over a longer follow-up period, and (ii) assess whether specific cognitive domains are differentially affected in PD patients with self-reported symptoms suggestive of RBD.

2. Methods

2.1. Study participants

PPMI is a prospective cohort study of PD patients untreated at baseline. Study aims, methodology, and details of study assessments have been published elsewhere [9] and are available on the PPMI website (<http://www.ppmi-info.org/study-design>). At enrollment, PD patients were required to (i) meet established motor criteria for PD diagnosis, (ii) have been diagnosed within two years of study enrollment, (iii) have dopamine transporter deficit on SPECT imaging, (iv) be untreated for PD, and (v) be dementia-free based on the site investigator's clinical assessment. At each follow-up in-person assessment, the diagnosis of PD was confirmed or revised based on the investigator's impression, using a structured diagnostic criteria form.

Data downloaded from www.ppmi-info.org/data on June 30, 2015 was used for this analysis. At that time, enrollment was complete. Baseline data were available for 423 participants and follow up assessments, including complete neuropsychological test data, at 1-year, 2-year, and 3-year follow-up, were available on 389, 366, and 196 participants respectively.

2.2. Assessments

2.2.1. Cognitive tests—At baseline and each annual follow-up visit, the following cognitive tests were administered as measures of the specified cognitive domain:

- i. Montreal Cognitive Assessment (MoCA) [10]: general cognition
- ii. Symbol Digit Modalities Test (SDMT) [11]: processing speed/attention
- iii. Phonemic fluency [12] (number of words generated starting with letter F): executive function
- iv. Semantic fluency [Esupp-ref1] (number of words generated for animals, vegetables, fruit): executive function/working memory
- v. Letter-Number Sequencing: executive function/working memory
- vi. Hopkins Verbal Learning Test-Revised (HVLT-R) [Esupp-ref2], immediate and delayed free recall and recognition: verbal memory
- vii. Benton Judgment-of-Line-Orientation (JOLO) 15-item (split-half) version [Esupp-ref3]: visuospatial function

Participants were classified as having mild cognitive impairment (MCI) on a given visit if they had 2 neuropsychological test scores > 1.5 SD below the standardized mean [Esupp-ref4].

2.2.2. Sleep assessments—The RBD Sleep Questionnaire (RBDSQ) [Esupp-ref5,6] was used as a measure of possible RBD (pRBD i.e., a history of dream enactment suggested by questionnaire response, but not confirmed with clinical interview/polysomnogram) This 10-item questionnaire probes subjectively-experienced symptoms of RBD. Scores range from 0 to 13. A score of 6 maximizes sensitivity/specificity for RBD in the PD population [Esupp-ref6] and was considered consistent with pRBD in this study. The only other measure of sleep included in PPMI is the MDS-UPDRS item-1.7 [Esupp-ref7], which asks “Over the past week have you had trouble going to sleep or staying asleep ...”. Response on this question is a measure of self-reported insomnia. Possible responses range from 0 to 4. This variable was dichotomized into those without (response = 0) vs. with sleep problems (response = 1).

2.2.3. Other assessments—Depression was assessed with the 15-item-Geriatric Depression Scale (GDS-15) [Esupp-ref8]. Visual hallucinations and other psychotic features (known associations with both RBD and cognitive impairment in PD [Esupp-ref9]) were assessed with MDS-UPDRS item 1.2. This variable was dichotomized into those without (response = 0) vs. with hallucinations/psychosis (response = 1). The Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part III score [Esupp-ref7] was the measure of motor function administered. Given differences in motor subtype reported in PD with RBD compared to those without [Esupp-ref10], the MDS-UPDRS part III score was used to derive tremor dominant, postural instability gait disorder, and indeterminate motor subtypes as previously described [Esupp-ref11,12]. Odor identification

was assessed using the University of Pennsylvania Smell Identification Test (UPSIT) [Esupp-ref13] with lower scores reflecting poorer olfactory function.

2.3. Statistical analysis

Baseline demographics and PD disease characteristics were summarized using descriptive statistics. Normality assumptions were checked whenever statistical procedures required normality assumption and non-parametric statistical tests were chosen as appropriate. All statistical tests were 2-sided. Statistical significance was set at $p < 0.05$. Analyses were conducted with SPSS (version-22).

The relationship between baseline pRBD and rate of cognitive decline was examined with linear mixed-effects models [Esupp-ref14], which account for correlations among repeating measures and variable length of follow-up. The predictive ability of pRBD on cognitive decline was examined through its interactions with visit time, representing the effect of baseline pRBD on change in cognitive scores over time. In each model, the independent variable was presence/absence of pRBD at baseline, visit, and visit*pRBD interaction term. The repeated measures of cognitive test scores were the dependent variables. Presence/absence of pRBD and covariates were treated as fixed effects. The intercept was treated as a random effect. Co-variables included baseline cognitive test score, disease duration at baseline, and variables established to be risk factors of cognitive decline in early PD (baseline age, MDS-UPDRS III score, UPSIT, sex, and years of education) [Esupp-ref15]. Baseline GDS-15 score was also examined as a co-variate.

The relationship between baseline pRBD and occurrence of MCI was examined with generalized estimating equations (GEE). This type of model accounts for reversion to normal that can occur in individuals with MCI and accounts for correlations among repeated measures of the outcome. Co-variables included were as specified above.

Sensitivity analyses: two alternate definitions of pRBD were examined as the independent variable in mixed effects models as delineated above: (i) response of “yes” on 2 of questions 6.1–6.4 of the RBDSQ (they query core features of RBD and may have a greater specificity [Esupp-ref16]), and (ii) RBDSQ score as a continuous variable.

3. Results

Baseline demographic and clinical characteristics are presented in Table 1. Baseline Hoehn&Yahr stage was either 1 ($n = 186$; 44%) or 2 ($n = 235$; 56%). PD patients with pRBD were more likely to have MCI. They had more depressive symptoms and visual hallucinations/psychosis, though these were in general of low prevalence in the cohort at baseline.

Baseline performance on the cognitive tasks among participants with vs. without pRBD are shown in Supplemental table-1. At baseline, those with pRBD performed worse on the SDMT, HVLt-R delayed free recall, JOLO, and semantic fluency.

On follow-up, baseline pRBD was associated with cognitive decline (Table 2). The MoCA score of PD patients with pRBD at baseline declined by 0.34 points per year more than in

those without pRBD ($p = 0.002$). The effect of pRBD on rate of cognitive decline was equivalent to the effect a 7-year increase in age would have on the MoCA score. Regarding specific cognitive tests, PD patients with pRBD experienced significantly greater declines in verbal memory and attention (SDMT) over time (Table 2).

Similar results were found when RBDSQ score was included in the model as a continuous variable: for each 1-point increase in baseline RBDSQ score, MoCA declined by -0.03 points ($p < 0.001$). The association between pRBD and global cognition was not different when the alternate pRBD definition was used as the independent variable in the linear mixed effects model ($\beta = -0.23$ (95% CI = $-0.42, -0.042$), $p = 0.016$). Adding depression to the models did not significantly alter the findings (data not shown).

In the GEE model, the odds of MCI at any time point during follow-up was significantly greater among those with pRBD at baseline compared to those without pRBD (OR = 2.08, $p = 0.002$, 95% CI 1.31–3.32). In one participant with pRBD at baseline, the diagnosis was revised to dementia with Lewy bodies on follow-up.

While insomnia was more common in those with pRBD at baseline compared to those without (Table 1), it was not independently associated with rate of change in MoCA score ($p = 0.14$) or any other cognitive measures (data not shown). Similarly, presence of insomnia did not alter the relationship between pRBD and cognitive measures in any of the models examined.

4. Discussion

In this study of early PD patients untreated at baseline, we found significant associations between pRBD at baseline and rate of cognitive decline over up to three years. Patients with pRBD had greater rates of decline in measures of global cognition, as well as measures of attention and verbal memory specifically. They were significantly more likely to meet criteria for MCI during follow-up.

The presence of RBD has several important prognostic implications. In individuals without a diagnosable neurologic disorder, RBD is highly associated with emergence of a neurodegenerative disorder, most often PD or DLB [Esupp-ref17]. Among those with already-established PD, RBD has been associated with greater rates of cognitive decline in more advanced PD cohorts [Esupp-ref18–20]. This study extends this association to early disease stages.

Regarding mechanisms that might explain the association between pRBD and cognitive decline, we consider two possibilities. One is that pRBD affects sleep quality/content, which in turn could lead to cognitive dysfunction through various mechanisms [Esupp-ref21]. While some studies have reported worse subjective sleep in PD patients with RBD [Esupp-ref22], this has not been demonstrated with objective measures of sleep in a large cohort of PD patients with RBD [Esupp-ref23]. While the patients with pRBD in our cohort were more likely to report insomnia, there was no independent association between insomnia and rate of cognitive decline. However this remains a possibility particularly since measures of

self-reported sleep quality were limited in this study, and no objective measures were available.

The second possibility relates to the neural substrate of RBD, and whether it might account for both RBD and cognitive dysfunction. For example, it is possible that the presence of RBD in de novo PD is a reflection of more severe neurodegeneration that also leads to greater rates of cognitive decline. Brainstem regions hypothesized to be involved in RBD pathophysiology [Esupp-ref24], such as the peri-locus coeruleus, are adjacent to noradrenergic pathways that may mediate cognition, particularly attention [Esupp-ref25]. Findings of greater cholinergic denervation in PD patients with RBD compared to those without [Esupp-ref26], and the well-established mediation of cognition (particularly verbal memory) by cholinergic pathways, are also in line with this. Thus, RBD in early PD may be a marker of more severe neurodegeneration with involvement of multiple neurotransmitter systems and brain regions that also subserve cognition. Indeed, PD patients with RBD show several neuroanatomic and electrophysiologic abnormalities suggestive of more advanced neurodegeneration compared to those without including greater slowing on awake EEG [Esupp-ref27] and smaller thalamic volume [Esupp-ref28]. Furthermore, non-demented PD patients with RBD share a clinical manifestation strongly associated with PD dementia: visual hallucinations [Esupp-ref9,29].

Study limitations include lack of interview-based assessment and polysomnographic characterization of nocturnal sleep. The RBDSQ is a screening tool that reflects subjective recall and interpretation, by the patient, of dream content/movements in sleep. It has low specificity in some settings [Esupp-ref30], and does not allow for delineation of the underlying etiology of nocturnal motor symptoms. Other disorders, such as obstructive sleep apnea (OSA), could account for the symptom burden reported [Esupp-ref31], and OSA is associated with cognitive impairment [Esupp-ref32]. However, only a small minority of individuals in the PPMI cohort had a reported history of OSA [Esupp-ref33], so contribution of OSA to our findings is likely minimal. Since non-differential diagnosis misclassification (as would be likely here) biases results toward the null, we may have underestimated the association between RBD and cognitive decline. Future studies examining the association between polysomnogram-verified RBD and other aspects of nocturnal sleep and cognitive course in early PD are needed.

In summary, early PD patients with pRBD experience greater rates of cognitive decline compared to those without pRBD, specifically on measures of attention and verbal memory. Mechanisms behind this association require further study. If our findings are confirmed, RBD may be useful to incorporate into models aiming to predict cognitive decline/dementia in PD. This may be useful in identifying which patients are candidates for specific interventions to prevent cognitive decline or development of dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2016.03.006>.

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Table 1

Baseline demographic and clinical characteristics of the entire cohort and in participants with and without possible REM sleep behavior disorder (pRBD; RDBSQ 6).

Variable	Entire cohort (n = 423)	Group with pRBD (n = 108)	Group without pRBD (n = 315)	p-value (between-group difference)
Age at baseline visit in years (mean (SD))	61.71 (9.73)	61.90 (9.86)	61.65 (9.70)	0.81 ^c
M:F (n)	277:146	79:29	198:117	0.052 ^c
Education in years (mean (SD))	15.54 (2.99)	15.28 (2.88)	15.63 (3.03)	0.29 ^c
Disease duration in years (median (IQR))	0.33 (0.17–0.67)	0.25 (0.17–0.59)	0.34 (0.25–0.67)	0.11 ^d
Insomnia (MDS-UPDRS 1.7 1), n (%) ^a	225 (53.19)	70 (64.81)	155 (49.21)	0.005 ^e
RDBSQ score (median (IQR))	4 (2–6)	3 (2–4)	8 (7–9)	0.0001 ^d
Mild cognitive impairment (by MDS Level 1 Criteria, n (%)) ^b	44 (30.34%)	18 (16.67%)	26 (8.25%)	0.013 ^e
Geriatric Depression Scale-15-score	2 (1–3)	2 (1–4)	2 (0–3)	0.0007 ^d
Hallucinations/psychosis (MDS-UPDRS item 1.2 1), n (%)	13 (3.07)	7 (6.48)	6 (1.9)	0.017 ^e
University of Pennsylvania Smell Identification Test (UPSIT) (mean, (SD))	22.35 (8.23)	20.861 (8.45)	22.86 (8.10)	0.03 ^c
MDS-UPDRS Part III (Motor Exam) (mean, SD)	20 (14–26)	21.99 (8.76)	20.52 (8.88)	0.14 ^c
Motor subtype, n (%)				0.68 ^e
Tremor dominant	299 (70.85)	73 (67.59)	226 (71.97)	
Postural Instability/Gait disorder	76 (18.01)	22 (20.37)	54 (17.20)	
Indeterminate	47 (11.14)	13 (12.04)	34 (10.83)	

^aThere was missing data for the MDS-UPDRS 1.7 item for 1 participant in the pRBD group.

^bThere was missing MCI categorization for 8 participants at baseline, 2 in the group with RBD and 6 in the group without RBD.

^cBy two-sample *t*-test.

^dBy Wilcoxon Rank-Sum test.

^eBy Chi-squared test.

Table 2

Results of linear mixed effects models examining the effect of possible REM sleep behavior disorder on change in cognitive scores.^a

Dependent Variable	β -coefficient (95% CI)	p-value
MoCA	-0.34 (-0.54, -0.13)	<0.001
Symbol Digit Modalities Test	-0.69 (-1.30, -0.09)	0.024
HVLT-R delayed free recall	-0.21 (-0.41, -0.013)	0.037
HVLT-R recognition discrimination	-0.15 (-0.35, 0.05)	0.150
Phonemic fluency (letter F)	-0.29 (-0.66, -0.08)	0.121
Benton Judgment of Line Orientation	-0.19 (-0.52, 0.15)	0.267
Letter-Number Sequencing	-0.12 (-0.30, -0.06)	0.190
Semantic fluency (sum of animals, vegetables, fruits)	-0.04 (-0.69, 0.61)	0.899

^aIn these models, RBDSQ - 6 is the independent variable and the cognitive score is the dependent variable, with age, sex, education, baseline MDS-UPDRS III score, baseline UPSIT score, and baseline cognitive score as co-variates.