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REM Sleep Behavior Disorder, as assessed by the RBDSQ, in G2019S LRRK2 mutation PD and unaffected carriers

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Abstract

Background—Rapid eye movement sleep Behavior Disorder occurs with idiopathic Parkinson disease (PD), and often precedes PD. Its frequency in *LRRK2*-PD and utility as a pre-clinical marker has not been established.

Methods—144 idiopathic PD, 142 *LRRK2* G2019S mutation PD, 117 non-manifesting carriers, 93 related non-carriers, and 40 controls completed the Rapid eye movement sleep Behavior Disorder Screening Questionnaire.

Results—30.6% idiopathic PD, 19.7% *LRRK2*-PD, 6% non-manifesting carriers, 20.4% related non-carriers, and 15% controls met cut-scores. The likelihood of abnormal scores was decreased in *LRRK2*-PD vs. idiopathic PD (OR=0.55, p=0.03), non-manifesting carriers vs. related non-carriers (OR=0.25, p<0.01), and PD <3 years duration, 1/19 *LRRK2*-PD vs. 14/41 idiopathic PD (p<0.05).

Conclusions—There is a lower frequency of abnormal Questionnaire scores in *LRRK2*-PD, especially in early *LRRK2*-PD, and in non-manifesting carriers. Therefore, the Rapid eye

movement sleep Behavior Disorder Questionnaire is unlikely to serve as a pre-clinical marker for phenoconversion to PD.

Keywords

Parkinson's disease; LRRK2; REM Behavior Disorder; RBDSQ; pre-clinical

INTRODUCTION

In the search for markers of pre-clinical parkinsonism, REM sleep behavior disorder (RBD) holds promise, as it is highly specific for phenoconversion to parkinsonism. As many as 90% of RBD cases develop a synucleinopathy, either idiopathic PD (IPD), Parkinson disease with dementia, dementia with Lewy bodies, or multiple system atrophy[1–4]. The time course to motor phenoconversion may exceed 10 years[3, 5], suggesting a long at-risk "pre-clinical" period during which potential therapeutics might be applied to lessen pathologic burden before development of full-fledged clinical disease[6, 7]. The gold-standard assessment for RBD is polysomnography (PSG). However, questionnaires regarding sleep behavior have good correlation with cases diagnosed in sleep laboratories,[8] and are more practical as screening tools. Harboring the G2019S *LRRK2* mutation is also a marker of pre-clinical disease, but only a third of carriers develop PD in their lifetimes [9, 10]. Therefore, combining a questionnaire marker for RBD with carriage of the *LRRK2* mutation might detect individuals who are at higher risk for phenoconversion. The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)[8] is one such questionnaire. In a smaller group of LRRK2-PD, there was a trend for RBDSQ abnormalities to be less frequent in LRRK2-PD than IPD[32]. Further, in a subset of the population evaluated here, continuous RBDSQ scores did not differ between carriers without PD (non-manifesting carriers (NMC)) and family members without PD (non-carrier family members, NCF)[15]. Herein we report the largest group of G2019S mutation LRRK2-PD assessed with RBDSQ, and because of the sample size, are able to report on a subgroup with early disease.

METHODS

536 participants from the *LRRK2* Ashkenazi Jewish Consortium centers in Tel Aviv (Tel Aviv Medical Center, TA n=249,) and New York (Mount Sinai Beth Israel, MSBI n=155, and Columbia University Medical Center, CU n=155), self-administered the RBDSQ, a questionnaire that evaluates frequency of dreams and nocturnal behavior, self and bed partner injurious behavior, specific movements and activities during sleep, nocturnal awakenings and overall sleep quality. Subjects included 144 PD without G2019S or any of the eight major Ashkenazi Jewish *GBA1* mutations (IPD), 142 G2019S mutation carriers with PD (LRRK2-PD), 117 G2019S mutation carriers without PD (NMC), 93 non-PD, non-mutation-carrying family members (NC-F), and 40 unrelated controls. Continuous scores from a subset of the RBDSQ data comparing NMC to NC-F were previously reported.[15]

Univariate demographic and RBDSQ comparisons were performed using Wilcoxon rank sum and Fisher's exact or Chi-squared tests both for the groups overall and evaluating factors that might be related to RBD. Generalized estimating equation (GEE) logistic

regression models evaluated likelihood of RBD by the RBDSQ cutoff-scores (defined as ≥6 for PD[37] and ≥5 for non-PD[8]), and adjusted for age, gender, UPDRS-III, and site (NY or TA), accounting for correlation between family members.

Further secondary analyses were performed within groups to determine whether features segregated with RBD in the LRRK2-PD and IPD groups, including duration of disease, UPDRS-III, motor subtype (postural instability gait predominant, PIGD)[16], Montreal Cognitive Assessment (MoCA) and hyposmia (defined as <15th percentile for age and gender with the 40-item University of Pennsylvania Smell Identification Test (UPSIT)).

RESULTS

Demographics (Table 1)

LRRK2-PD were more likely to be male than controls and NMC but not than IPD or NC-F. Mean age of IPD (64.9 ± 11.3) was not different from LRRK2-PD (67.2 ± 9.8). Both IPD and LRRK2-PD were older than NMC (53.3 ± 15.9) and NC-F (52.8 ± 18.5). IPD were younger than controls (69.8 ± 10.6) but LRRK2-PD were not. Age at onset did not differ between IPD and LRRK2-PD (58.0 ± 10.9 and 57.4 ± 11.0), nor did UPDRS-III, but duration of PD was longer in the LRRK2-PD group (7.36 ± 7.53 vs. 9.98 ± 7.10 years) ($p<0.01$).[17]

RBDSQ Scores (Table 1)

30.6% of IPD met criteria for abnormal RBDSQ score vs. 19.7% of LRRK2-PD, 6.0% of NMC, 20.4% of non-carrier family members and 15.0% of controls. In the main GEE model adjusting for age, site (NY vs. TA) and gender, the likelihood of having abnormal RBDSQ was decreased in LRRK2-PD vs. IPD (OR=0.55, p=0.03) and increased in LRRK2-PD vs. NMC (OR=3.24, p=0.01) but not different in LRRK2-PD vs. controls (OR 1.50, p=0.42). It was less in NMC than NC-F (OR=0.25, $p<0.01$), and did not differ between NMC and controls (OR=2.17, p=0.21). Among subjects with early PD (<3 years duration), abnormal scores were present in only 1/19 cases with LRRK2-PD and in 12/41 cases with IPD ($p<0.05$). In post hoc univariate comparisons in IPD (Table 2), abnormal RBDSQ scores were associated with worse UPSIT score, PIGD phenotype. In LRRK2-PD, duration of disease and anxiety were significant.

There was no difference between the IPD and LRRK2-PD groups in current use of medications implicated as triggers of RBD, such as MAO-B inhibitor, tricyclic antidepressant (TCA), or selective serotonin reuptake inhibitor (SSRI) (IPD=82.6% vs. LRRK2-PD=73.9%, p=0.07) or those used for treatment of RBD, such as clonazepam (IPD=6.9% vs. LRRK2-PD=7.8%, p=0.80). In a GEE model limited to patients with PD adjusting for reported current use of trigger or treatment medication, age, site, gender, and disease duration, there was no change in the direction or the overall magnitude of the odds ratio for abnormal RBDSQ between LRRK2-PD and IPD.

DISCUSSION

RBD should meet several criteria to serve as a marker to detect a highly at-risk LRRK2-PD subset: it should 1) have easily applied and relevant instruments that discern the marker and these should 2) be abnormal in at least a subset of affected individuals in the disease of interest (LRRK2-PD), 3) be abnormal early in disease, and 4) be present in at least a subset of NMC prior to phenoconversion. While PSG is the gold-standard, the RBDSQ is readily applied and inexpensive and, in our study, the proportion of IPD with RBD was similar to another study[18]. However, while present in LRRK2 carriers, abnormal RBDSQ scores occurred in only one of the 19 LRRK2-PD with early disease, compared with 14/41 IPD (p=0.05). This supports that even in a cross-sectional *LRRK2* study, abnormal RBDSQ is not a frequent feature in early LRRK2-PD. Further, the paucity of NMC who meet criteria for RBDSQ does not allow for assessment of a subcluster, which might be present in a small subgroup of NMC close to phenoconversion.[19]

The decreased frequency of abnormal RBDSQ scores in LRRK2-PD compared with IPD is consistent with its infrequency in certain genetic forms of PD. RBD is more common in IPD with neuropsychological deficits,[20–24] akinetic-rigid disease,[25–27] orthostatic changes,[3, 28] and greater heart-rate variability[29]. With the exception of MoCA, which did not correlate with abnormal RBDSQ scores in this cohort, we observed similar trends suggesting possible subgroups relating RBD and non-motor features in both IPD and LRRK2-PD. In the IPD group, RBDSQ was associated with worse olfaction and PIGD phenotype. In the LRRK2-PD group, RBD was associated with more prominent trait ($p<0.01$) and state ($p=0.03$) anxiety. [30,31,19]

There are several limitations to our study. Measurement of RBD by questionnaire does not capture RBD in the same manner as the gold standard polysomnography, and the RBDSQ is just one of several validated questionnaires, each with their respective strengths. Additionally, we did not require sleep partners to participate in all questionnaires, and the information regarding whether a bed partner participated in the questionnaire was not consistently noted, so that a proportion of cases might be underestimated or mis-classified. However, in support of our methodology and findings, our results are consistent with the trends seen using other assessment methods, where the rates of RBD were lower in LRRK2-PD (range: 11.1–21.2%) compared to IPD (range: 29 to 42%)[32–34]. Further, the RBDSQ performs well overall, particularly with normal volunteer controls, with 96% sensitivity and 92% specificity[8]. This group is more similar to NMC, NC-F and controls than a symptomatic RBD group would be. Only one study reports the gold standard for RBD, PSG, and reports six cases of LRRK2-PD with RBD[14]. However rates were not compared between LRRK2-PD and IPD. Further, PSG is time-intensive and expensive. We cannot exclude that rates might differ were PSG utilized, as clinical reports may underreport as many as half of the cases[36, 37].

In summary, RBD, as measured by RBDSQ, is not a common feature of early LRRK2 PD and *LRRK2* gene carrier status overall. Longitudinal study with PSG will facilitate a more precise assessment of the association between RBD and *LRRK2* expression over time.

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Table 1

Demographics and REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) Scores

	IPD[a]	LRRK2-PD[b]	NMC[c]	NC-F[d]	Control[e]
n	**144**	**142**	**117**	**93**	**40**
Women %	35.4%[cde]	45.8%[ce]	59.8%[ab]	50.5%[ae]	72.5%[abd]
Age years	64.9 ± 11.3[cde]	67.2 ± 9.8[cd]	53.3 ± 15.9 [abe]	52.8 ± 18.5 [abe]	69.8 ± 10.6[acd]
UPDRS-III	20.1 ± 11.8[cde]	21.1 ± 13.1[cde]	2.5 ± 3.5[ab]	2.5 ± 3.5[ab]	2.1 ± 3.4[ab]
Age onset	58.0 ± 10.9	57.4 ± 11.0	-	-	-
PD Duration years	7.4 ± 7.5[b]	10.0 ± 7.1[a]	-	-	-
RBDSQ score median (IQR)	4.0 (2.0–7.0)[cde]	3.0 (2.0–5.0)[cde]	2.0 (1.0–3.0)[ab]	2.0 (1.0–4.0)[ab]	2.0 (1.0–4.0)[ab]
RBD+ %	30.6%[bcde]	19.7%[ac]	6.0%[abd]	20.4%[ac]	15.0%[a]

Odds Ratios for Abnormal RBDSQ Scores Among

All Groups **

n = 536	**OR**	**95% CI**	***P***
Age	1.01	.99–1.02	0.56
Sex (Women)	0.64	.41–1.01	0.06
Site (NY)	1.57	.97–2.54	0.07
Group:			
Control (ref)	---	---	---
IPD	2.75	.03–7.35	0.04
LRRK2-PD	1.50	.56–4.04	0.42
NMC	0.46	.14–1.54	0.21
NC-F	1.89	.65–5.51	0.25
*Further group comparisons**			
IPD vs. LRRK2-PD	1.83	.05–3.18	0.03
NMC vs. LRRK2-PD	0.31	.13–0.75	0.01
NC-F vs. LRRK2-PD	0.80	.40–1.59	0.52
NMC vs. NC-F	0.25	.10–0.61	<0.01

Odds Ratios for RBDSQ Restricted to PD Groups

n = 275	OR	95% CI	*P*
IPD vs. LRRK2-PD	2.38	.29–4.38	<0.01
Age	1.01	.99–1.04	0.34
Sex (Women)	0.54	.29–1.00	0.05
Site (NY)	1.37	.75–2.52	0.31
Duration	1.08	.03–1.14	<0.01
UPDRS-III	0.99	.97–1.02	0.20

* Additional group comparisons were deduced from the main model; Values provided are number (%) or mean ± SD, as appropriate, unless otherwise stated; Superscripts denote significant differences from the superscripted group ($p<0.05$); ORs from GEE models adjusted for age, site (NY vs. Israel), gender and family membership Definitions: LRRK2-PD=*LRRK2* G2019S mutation carriers with PD; IPD=idiopathic PD; NMC=*LRRK2* mutation carriers without PD; NC-F=non-carrier family members; UPDRS-III=Unified Parkinson Disease Rating Scale Motor Score; RBDSQ=REM Sleep Behavior Disorder Screening Questionnaire; RBD+=total RBDSQ score ≥ 5 (non-PD) and total RBDSQ score ≥ 6 (PD).

** In post-hoc analysis using the main GEE model to assess site differences, all differences from the main model were maintained when limited to participants from either NY or TA, except that NMC from NY were not different from LRRK2-PD (OR=0.34, p=0.07) or NC-F (OR=0.30, p=0.06) and, although the magnitude of the OR was maintained, in TA the odds of RBD was not significantly reduced in LRRK2-PD vs. IPD (OR=0.73, p=0.49).

Table 2

Features associated with RBDSQ Cut-scores in Parkinson disease

	RBDSQ+	RBDSQ-	*P*
LRRK2-PD (n=142)	28 (19.7%)	114 (80.3%)	---
Women	9 (32.1%)	56 (49.1%)	0.14
Age	68.2 ± 9.1	67.0 ± 10.0	0.72
Duration	14.6 ± 7.6	8.8 ± 6.5	<0.01
UPSIT Score (125)	20.9 ± 8.6	23.5 ± 8.6	0.19
Hyposmia	15 (60.0%)	53 (53.0%)	0.53
UPDRS-III (135)	24.2 ± 12.9	20.3 ± 13.1	0.07
PIGD phenotype (133)	22 (81.5%)	67 (63.2%)	0.11
MoCA Score (131)	24.8 ± 3.6	25.4 ± 2.8	0.67
STAI (42)			
State	43.4 ± 11.8	33.7 ± 13.4	0.03
Trait	48.8 ± 14.6	33.4 ± 11.7	<0.01
IPD (n=144)	44 (30.6%)	100 (69.4%)	---
Women	11 (25.0%)	40 (40.0%)	0.08
Age	67.5 ± 10.1	63.8 ± 11.7	0.06
Duration	7.8 ± 6.6	7.2 ± 7.9	0.48
UPSIT Score (117)	17.1 ± 7.6	19.5 ± 6.9	<0.05
Hyposmia	26 (86.7%)	65 (74.1%)	0.21
UPDRS-III (142)	21.2 ± 12.0	19.7 ± 11.8	0.51
PIGD phenotype (141)	31 (70.5%)	45 (46.4%)	<0.01
MoCA Score (134)	24.7 ± 3.2	25.1 ± 3.9	0.28
STAI (36)			
State	40.2 ± 7.1	34.6 ± 10.5	0.06
Trait	38.6 ± 9.8	36.9 ± 12.6	0.48

Values provided are number (%) or mean ± SD, as appropriate, unless otherwise stated.

RBD+=total RBDSQ score ≥5 (non-PD) and total RBDSQ score ≥6 (PD).; LRRK2-PD = *LRRK2* G2019S mutation carriers with PD; IPD = idiopathic PD; UPSIT = University of Pennsylvania Smell Identification Test; Hyposmic = UPSIT percentile score < 15; UPDRS-III = Unified Parkinson Disease Rating Scale Motor Score; PIGD = Postural Instability and Gait Disorder subtype; MoCA = Montreal Cognitive Assessment; STAI = State-Trait Anxiety Inventory