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The association between restless legs syndrome and premotor symptoms of Parkinson's disease

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ABSTRACT

Background: Previous studies regarding the association between restless legs syndrome (RLS) and Parkinson's disease (PD) have produced contradictory results. However, the time frame between them has varied across these studies, and also, the longitudinal trajectroy of RLS symptoms has not been considered.
Objective: To investigate if transient or continuous/recurrent RLS identified by questionnaire are associated with the premotor symptoms of PD.
Methods: The study population comprised 16,636 men in the Health Professional Follow-Up Study, who answered questions regarding RLS symptoms in both 2002 and 2008, and were not diagnosed with PD. Outcomes were self-reported constipation, possible REM sleep behavior disorder (pRBD) in 2012 and smell identification test score in 2014.
Results: RLS was associated with increased odds of constipation, but only continuous/recurrent RLS status was associated with higher odds of having pRBD. RLS was not significantly associated with olfactory scores.
Conclusion: In this large-scale longitudinal study, we found moderate associations between the presence of RLS and increased odds of having constipation and pRBD.

1. Introduction

Restless legs syndrome is a common sensorimotor disease characterized by an urge to move one's legs when at rest [1]. The mechanism of RLS is poorly understood, but some researchers have reported a significant dopaminergic system deficit in the basal ganglia of patients with RLS [2,3]. In addition, dopamine agonists, which are drugs typically used for Parkinson's disease, provide symptomatic relief. The reported prevalence of RLS in the PD population ranges from 5.5% to 27% in Europe and America [4], which is higher than the 3.9% to 14.3% observed in the background population [5–8].

There are, however, some negative RLS and PD association results. For example, presynaptic dopamine imaging showed no abnormalities in 29 RLS patients [9], and autopsy assessments found no Lewy bodies, the key pathology of PD, in brain and spinal cord tissues of four idiopathic RLS cases [10]. However, some prodromal PD symptoms are known to occur more than a decade prior to diagnosis [11,12], and no studies have assessed RLS symptoms as possible initial signs of PD etiology. Another source of contradictory results could be a different longitudinal trajectory of RLS symptoms among cases. According to previous studies [13–15], 30–60% of patients with RLS are self-limiting in 2–10 years of follow-up, and the transient RLS etiology may not be the same as continuous or recurring.

We were interested in whether RLS is a sign of early phase neurodegeneration due to sharing common mechanisms with PD. Using data from a prospective cohort study, we conducted an analysis to identify associations between RLS symptom questionnaire responses, and well-recognized prodromal PD symptoms. The questionnaires were given twice with a 6-year interval in-between, and outcomes were idiopathic rapid eye movement sleep behavior disorder (RBD) and hyposmia, assessed a decade after the initial RLS questionnaire.

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Table 1
Summary characteristics of the study population by RLS status in 2002 and 2008.

	RLS status in 2002 and 2008			
	No RLS (n = 15,362)	Transient (n = 441)	Developed (n = 601)	Continuous/ Recurrent (n = 232)
Age (years-old)	65.43(7.27)	66.85(7.53)	66.38(7.31)	66.91(7.71)
Race				
- South European (Mediterranean), %	25	27	26	27
- Scandinavian, %	11	10	12	11
- Other Caucasian, %	60	60	59	58
- Non-Caucasian, %	3	3	4	3
Smoke status				
- Never, %	46	44	44	42
- Past or unknown, %	51	53	54	54
- Current, %	3	2	3	4
BMI kg/m2	26.02(4.23)	26.42(4.96)	26.85(3.59)	26.56(4.05)
2002 Total Activity Mets/Week	39.17(40.53)	36.71(38.80)	38.41(42.00)	37.64(40.36)
Alcohol, gm	13.65(16.15)	11.95(14.92)	12.33(15.73)	13.44(17.73)
Energy-adjusted Caffeine Intake, mg	153.0(151.7)	149.9(152.6)	150.7(155.3)	129.6(126.7)
Energy-adjusted Lactose Intake, mg	14.89(12.28)	15.99(13.44)	14.74(11.07)	16.16(14.21)
Constipation, %	23	28	30	32
pRBD, %	11	12	13	16
Constipation and pRBD, %	3	3	4	9

Values are means (SD) or percentages and are standardized to the age distribution of the study population.
Values of polytomous variables may not sum to 100% due to rounding.
RLS, Restless Legs Syndrome; BMI, Body Mass Index; pRBD, probable REM sleep behavior disorder.

2. Methods

The investigation was conducted with participants from the Health Professional Follow-Up Study (HPFS), a cohort beginning in 1986 with 51,529 US males in health professions, aged 40–75 years. Questionnaires were sent biannually asking about lifestyles and medical histories. Reports of newly diagnosed PD were verified by a neurologist specializing in movement disorders reviewing the medical records as previously described [16]. The cohort was defined as all men who responded to the RLS questionnaires in both 2002 and 2008 (n = 23,458), with the following exclusions: use of anti-depressant medication either in 2002 or 2008 (n = 948) (as the drugs could induce RLS [17]); PD diagnosis by 2012 (n = 283); lack of a sleep partner or missing information on pRBD questions (n = 5478); and missing bowel movement frequency (n = 113). Thus, 16,636 men were eligible for the study.

In agreement with the International RLS Study Group (IRLSSG) criteria [18], participants were considered to have RLS if they reported unpleasant leg sensations combined with motor restlessness and an urge to move legs, only occurring at rest and worse in the evening/night, and occurring more than five times per month. We considered four categories: control (RLS negative in both 2002 and 2008), transient RLS (RLS positive in 2002 but negative in 2008), developed RLS (negative in 2002 but positive in 2008), and continuous/recurrent RLS (positive in both 2002 and 2008).

The outcomes were having constipation and/or pRBD in the 2012 questionnaire. Constipation was defined as bowel-movement frequencies of every other day or less and/or laxative use at least twice per week. An individual was considered to have pRBD if he reported being told by his sleep partner that he acted out his dreams while sleeping at least three times in the past. This is the first question on the Mayo Sleep Questionnaire and was demonstrated to have 100% sensitivity and 95% specificity in a community-based sample for the diagnosis of polysomnogram-confirmed RBD [19].

In addition, all participants with constipation or pRBD in 2012 and a sample of age-matched controls who had neither of these symptoms were invited to complete the 12-item Brief Smell Identification Test (B-SIT; Sensonics Inc. Haddon Heights, NJ, USA) in 2014. Overall, 5249 men completed the test and were included in analyses of the association between RLS and olfactory scores.

All covariates were measured using the 2002 questionnaire; these included age (< 60, 60–64, 65–69, 70–74, 75–79, 80+), race (Scandinavian, Southern European, Other Caucasian, and Non-Caucasian), BMI (< 23, 23–24.9, 25–26.9, 27–29.9, 30+ kg/m^2), smoking status (never, former/unknown, current {cigarette 1–14/d, 15–24/d, 25−/d, unknown}), alcohol (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, 30+ g/d), caffeine intake (quintiles), lactose intake (quintiles), and physical activity level (quintiles).

In the statistical analysis, participant characteristics were summarized using proportions for categorical variables and means with standard deviation for continuous variables. The association between RLS status and the odds of having constipation or pRBD were tested using a logistic regression model, adjusting for the significant covariates by stepwise approach. The association between RLS and the smell test score was tested using a linear regression model, adjusted for the covariates and different recruiting groups. All analyses were conducted in SAS 9.4 (SAS Institute Inc. Carry, NC, USA) with a significance level of 0.05 (two-tailed).

The study received ethical approval from an Institutional Review Board (Approval number 2013P001843) and written informed consent was obtained.

3. Results

Among 16,636 participants, the prevalence of RLS was 4.1% in 2002 (n = 673), and 5.0% in 2008 (n = 833). Only one-third of RLS-positive men in 2002 were also positive in 2008 (n = 232), while 3.8% (n = 601) of the RLS-negative men in 2002 had become RLS positive in 2008. Their basic characteristics are described in Table 1. Age was the only significant confounder for the outcomes and was adjusted for in further analyses.

Having RLS in 2002 and/or 2008 was associated with higher odds of having constipation in 2012 compared to controls (transient RLS: OR 1.26, 95% CI [1.02, 1.56]; developed RLS: OR 1.38, 95% CI [1.15, 1.65]; continuous/recurrent RLS: OR 1.50, 95% CI [1.13, 1.99]; Table 2). The magnitude of association was similar across RLS groups. In contrast, continuous RLS, but not transient or newly developed RLS, was associated with pRBD (transient RLS: OR 1.01, 95% CI [0.75, 1.36];

Table 2
Number of cases and age-adjusted odds ratio of having the outcomes by RLS status compared with no RLS.

	RLS status			
Outcomes	Control (n = 15,362)	Transient (n = 441)	Developed (n = 601)	Continuous/ Recurrent (n = 232)
Constipation				
Case	3491	125	178	74
Odds ratio	1 (ref)	1.26 [1.02, 1.56]*	1.38 [1.15, 1.65]**	1.50 [1.13, 1.99]**
pRBD				
Case	1760	51	77	38
Odds ratio	1 (ref)	1.01 [0.75, 1.36]	1.14 [0.89, 1.45]	1.52 [1.07, 2.16]*
Both symptoms				
Case	503	15	22	21
Odds ratio	1 (ref)	0.99 [0.59, 1.67]	1.09 [0.70, 1.68]	2.83 [1.79, 4.48]**

* $p < .05$.
** $p < .01$.
RLS, Restless Legs Syndrome; pRBD, probable REM sleep behavior disorder.
Adjusted means of smell score for each categories or Restless Legs Syndrome adjusted with age groups and recruiting groups. Error bar indicates the standard deviation.
(p: ANCOVA)

developed RLS OR 1.14, 95% CI [0.89, 1.45]; continuous/recurrent OR 1.52, 95% CI [1.07, 2.16]). Men with continuous RLS also had significantly higher odds of having both constipation and pRBD (OR 2.83, 95% CI [1.79, 4.48]). In contrast, the mean olfactory score was similar in men with or without RLS ($p = .33$). The least square means and their standard errors were almost the same across groups (Fig. 1).

4. Discussion

We analyzed the association between RLS status in 2002/2008 and prodromal PD symptoms in the following years, constipation and pRBD in 2012, and olfactory function in 2014. The questionnaire results showed that 65.5% of people with RLS symptoms in 2002 didn't have symptoms by 2008. The prevalence of RLS in our study cohort and its self-remitting ratio agrees with the prior literature [13–15]. RLS history was significantly associated with increased risk of constipation. Although RLS is associated with many medical conditions [20], an increased prevalence of constipation has not been previously reported in RLS. However, constipation is a relatively non-specific symptom and thus constipation in RLS does not indicate a direct link to PD. We excluded people taking antidepressants that can cause RLS and constipation. But other drug use—e.g. dopamine agonists—can be a potential confounder.But the fact that groups with transient RLS also had constipation suggests that confounding by medication is an unlikely explanation.

Only one study has evaluated the relationship between RLS and RBD [21]. In a cross-sectional study, 6 (20%) of 30 patients with RLS were found to have pRBD, which was higher, but not significantly different than 13% (23/175) observed in controls. We did not find an association between transient RLS and pRBD. However, men with continuous/recurrent RLS had significantly greater odds of having pRBD. Moreover, continuous/recurrent RLS were strongly associated with having both pRBD and constipation, indicating a potential association between continuous/recurrent RLS and PD. Other than RLS status, age was significantly associated with pRBD in our cohort. A previous study also reported socioeconomic status, head injury, olfactory and taste dysfunction, and various cardiovascular risk factors as associated risk of pRBD [22]. This is important because a substantial proportion of patients with RBD seem to later develop synucleinopathy including PD. [22] Continuous/repeated RLS associated with pRBD may be further evidence to link RLS and PD. However, all groups, including the continuous RLS group, had similar olfactory identification scores. The lack of statistically significant differences should be interpreted with caution because the data on olfactory function were only available for a subset of the cohort. The timing may have also affected the result because olfactory loss is a relatively late symptom in the prodromal stage of PD compared to constipation and RBD [11,23]. Three other studies have applied various olfactory function tests for RLS patients and none could confirm a significant decline in olfactory abilities [24–26]. They were cross-sectional studies with relatively small numbers of patients ($n \leq 25$), and analyses were not adjusted for important factors such as age. A recent, large, population-based analysis ($n = 19{,}176$) reported a significant association between hyposmia and RLS (adjusted OR2.5, 95% CI [2.2–2.9]). It was not measured by olfactory tests and thus is subjective [27]. More data is needed to draw any conclusions about the association between olfactory function and RLS.

Previous studies had varied temporal ranges between RLS and PD. RLS is sometimes referred to as a complication or an early symptom of PD. Two cross-sectional studies pointed out that RLS is more likely to occur after PD onset [6,7]. One prospective cohort study found a higher incidence of PD in an RLS-positive group, but only for the first four years after the identification of RLS symptoms [28]. Furthermore, RLS in PD is reported to have a different phenotype from that in the general population [29], and is less-frequently noted in the family history of PD patients [6]. In a separate prospective cohort study including 100,882 US veterans, a higher incidence of PD was found in people with RLS who were followed for an average of 7.8 years [30]. Our research looking at the association between RLS and prodromal signs of PD casts more light on the possible association between RLS and PD. The magnitudes of the associations between RLS and constipation, and RLS and pRBD were moderate but consistent with the interpretation that RLS is a risk factor for PD.

Our study has several limitations. Firstly, we could not validate the exposures and outcomes by in-person examination. However, we used well-validated questionnaires for our assessments. Secondly, the analysis was conducted within a male-only cohort. Men are more susceptible to PD, while women are more susceptible to RLS [27,31]. Thus, it is plausible that correlations between RLS and PD could differ by gender. Thirdly the medication for the treatment of RLS was not recorded, so we could not eliminate the possibility of confounding by medication. But if medication affected the outcomes, the transient RLS group should not have higher odds of constipation, and in contrast, the developed group should have the same odds of pRBD with continous/reccurent RLS groups, but neither was observed. Finally, we assessed the association between RLS and PD prodromal signs, but not between RLS and PD incidence. However, our focus was on identifying whether RLS is an early indicator of the underlying common disease process in PD. The current study alone is not sufficient to draw a conclusion for RLS as a long-term PD risk. Recently we reported the premotor symptoms were associated with odds of PD exponentially to each other (OR up to 160 [72.8, 353] if concurrent constipation, pRBD, and hyposmia) in the nested case-control study of the same cohort [32]. Combined with the current results that continous/recurrent RLS was associated with both constipation and pRBD, the result is encouraging longer follow-up studies for RLS and PD incidence in the long-term.

Authors' roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.

H.I.: 1A, 1C, 2A, 2B, 3A, 3B
K.C.H.: 2C, 3B
X.G.: 3B

M.A.S.: 3B
A.A.: 1A, 1B, 2A, 2C, 3B
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Nothing to report

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Financial disclosure/Conflict of interest

Nothing to report.

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