



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 trajectory 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/m ²	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/m²), 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. Cary, 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];

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