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Subtle gait changes in patients with REM Behavior Disorder

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Abstract

Background—Many people with REM sleep behavior disorder have an underlying synucleinopathy, the most common of which is Lewy body disease. Identifying additional abnormal clinical features may help in identifying those at greater risk of evolving to a more severe syndrome. As gait disorders are common in the synucleinopathies, early abnormalities in gait in those with REM sleep behavior disorder could help in identifying those at increased risk of developing overt parkinsonism and/or cognitive impairment.

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Methods—We identified 42 probable REM sleep behavior disorder subjects and 492 controls using the Mayo Sleep Questionnaire and assessed gait velocity, cadence and stride dynamics with an automated gait analysis system.

Results—Cases and controls were similar in age (79.9 ± 4.7 & 80.1 ± 4.7, p= 0.74), UPDRS score (3.3 ± 5.5 & 1.9 ± 4.1, p=0.21) and Mini-Mental State Examination scores (27.2 ± 1.9 & 27.7 ± 1.6, p=0.10). A diagnosis of probable REM sleep behavior disorder was associated with decreased velocity (−7.9 cm/sec, 95%CI −13.8 to −2.0, p<0.01), cadence (−4.4 steps/min, 95%CI −7.6 to −1.3, p<0.01), and significantly increased double limb support variability (30%, 95%CI 6 – 60, p=0.01), greater stride time variability (29%, 95%CI 2 – 63, p=0.03) and swing time variability (46%, 95%CI 15 – 84, p<0.01).

Conclusions—Probable REM sleep behavior disorder is associated with subtle gait changes prior to overt clinical parkinsonism. Diagnosis of probable REM sleep behavior disorder supplemented by gait analysis may help as a screening tool for disorders of α-synuclein.

Keywords

REM Sleep Behavior Disorder; gait; gait variability

Introduction

REM Sleep Behavior Disorder (RBD) is closely associated with neurodegenerative diseases associated with abnormal accumulations of α-synuclein: Parkinson's disease (PD), Multiple System Atrophy (MSA) and Lewy Body Dementia (LBD)[1, 2]. The pedunculopontine tegmental nucleus (PPN), a brainstem nucleus involved in REM sleep control is also important in gait coordination and rhythmicity[3, 4,5]. Some[6] but not all [7] studies suggest that subjects with RBD and PD have more axial features, including differences in gait, compared to PD subjects without RBD.

RBD is highly specific to the synucleinopathies[1]; it frequently precedes the other symptoms of synucleinopathy, suggesting that RBD-associated loci may be affected early in the disease course. Iranzo and colleagues[8] demonstrated that 30% of RBD subjects with reduced ^{123}I-FP-CIT binding and substantia nigra hyperechogenicity on transcranial sonography studies progressed to PD, dementia with Lewy bodies or multiple system atrophy 2.5 years later. However such extensive evaluations are time consuming, expensive and not widely available. Similarly, polysomnography is expensive and labor intensive.

The use of simple and inexpensive tools may assist in identifying those with RBD as well as identifying unique phenotypes that lead to a greater mechanistic understanding of neurodegenerative diseases and aid in predicting the development of parkinsonism and/or cognitive impairment. For example probable RBD (pRBD), as determined by the Mayo Sleep Questionnaire (MSQ), has a sensitivity of 98–100% and specificity of 74–95% for polysomnogram-confirmed RBD[910] and pRBD predicts future PD and mild cognitive impairment amongst a cognitively normal population [11]. Given the association of α-synucleinopathies with RBD, we hypothesize that subjects with pRBD will have differences in gait compared to those without as measured by sensitive, automated gait analysis. We explored this in subjects with and without pRBD in a community sample without PD or cognitive impairment.

Methods

Study population

The Mayo Clinic Study of Aging (MCSA) is a prospective, population based study of randomly selected residents of Olmsted County, Minnesota, between the ages of 70 –89 at time of enrollment [12]. Of the 2050 subjects who agreed to undergo face-to-face evaluations, only those free of a diagnosis of dementia based on DSM-IV criteria were eligible for continued participation. To be included in the present analyses, subjects had to be able to follow the gait protocol, and have an informant who slept in the same room: this is a requirement of the Mayo Sleep Questionnaire (MSQ). From this group of 569 non-demented individuals with available information, an additional 31subjects were excluded: 18 with stroke, 2 with sub-dural hemorrhage, 3 with history of alcohol abuse, and 8 subjects with PD. Four subjects with probable obstructive sleep apnea were excluded because the syndrome produces false positive pRBD diagnoses [9]. The study protocol was approved by the institutional review board of the Mayo Clinic and Olmsted Medical Center and all subjects signed consent at enrollment.

Participant Evaluation

Physicians, nurses and neuropsychologists each performed in-person assessments. An expert physician performed a structured neurological exam including the modified Unified Parkinson's Disease Rating Scale Part III (UPDRS)[13] and mental status screening. Trained nurses administered the Clinical Dementia Rating scale, and psychometrists administered 9 tests of memory, language, executive function and visuospatial skills[12]. Z-scores for these cognitive domains were calculated using age- and education-matched norms. All clinicians including a board certified neuropsychologist met weekly to reach consensus on clinical diagnoses of cognitively normal, mild cognitive impairment and the dementias.

RBD Diagnosis

pRBD was diagnosed if an informant answered yes to question 1 of the MSQ: "Have you ever seen the patient appear to 'act out his/her dreams' while sleeping? (punched or flailed arms in the air, shouted or screamed)", but answered no to questions probing for obstructive sleep apnea, a disease which can also produce dream enactment behavior. Subjects who did not meet these criteria were considered as controls. The MSQ is available free for clinical and research purposes from: http://www.mayoclinic.org/sleep-disorders/research.html.

Gait Analysis

Gait analyses were performed using the GAITRite® system (Sparta, NJ, USA) on a 5.0 × 0.7 meter walkway. The system has established criterion validity for both temporal and spatial measures with intra-class correlation coefficients (ICC 0.69–.99), and good intra-class reliability for different gait speeds in both young and older adults (ICC 0.82–.99)[14–16]. Participants are instructed to walk at a normal pace with a one meter start up distance prior to stepping onto the mat. Each subject walked "up and back" once for a total of 10 meters. All gait parameters are automatically calculated by the system using the output from the each footfall detected by the mat and automatically averaged over the two times each subject traversed the length of the gait mat; further details are described elsewhere[14–16]. Gait variability, a measure of fluctuation in the gait cycle is computed automatically by the GAITRite system based on the average values over the 10 meter measurement.

Statistics

Descriptive statistics of medical, cognitive and unadjusted gait variables were compared between pRBD and control subjects. Based on the current literature using similar gait

analysis systems, we selected eleven spatiotemporal gait variables that represent unique dimensions of gait and those shown to be associated with synucleinopathies[17, 18 19–21]. Furthermore, this allowed us to assess the association between pRBD and specific gait dimensions. Most measures of stride-to-stride gait variability were not normally distributed. These parameters were log-transformed for analysis and then reverse-transformed for summary purposes. Because reverse-transformed values preserve relative, and not absolute, differences, they may reflect biased estimates of the absolute changes in units of the original measurements. Therefore, according to convention, we present these data as a percent difference between the groups. For example, stride time variability represents the amount of fluctuation that occurs from one stride cycle to the next. Thus a higher percent in stride time variability represents a greater amount of fluctuation or variability in the gait cycle in that group. We also performed a principal components analysis with varimax rotation of the eleven parameters in order to asses the orthogonal relationship of these gait parameters.

To assess the effect of pRBD on spatio-temporal gait patterns, we performed eleven separate multivariable linear regression analyses comparing pRBD and control subjects on each of the 11 gait parameters. In addition, we tested five different regression models to examine the roles of covariate factors. Model one adjusted for age and sex. Given the association between executive performance and gait [22, 23], model two additionally adjusted for subjects' executive function z-score. There were significant group differences in Beck Depression Inventory scores, and visuospatial performance. Because these differences might have influenced group differences in gait dynamics, in model 3 we also adjusted for these two variables in addition to all other covariates. Differences in gait might reflect the data from a subset of subjects with clinically evident parkinsonism, and not from the pRBD group as a whole. Therefore we repeated the models after excluding subjects with UPDRS scores above 4, table 3. For the few variables that violated the normality of residuals criteria, we calculated a non-parametric rank of variables model but the results were without significant changes in parameter estimates. No adjustments for multiple comparisons were made in these exploratory analyses. All analyses were performed using the SAS v.8.2 statistical package (Cary, NC).

Results

Table 1 outlines demographic, clinical and cognitive profiles between the groups. There were 42 pRBD subjects (81% male) and 492 normal controls (70% male). The two groups were similar ($p>0.05$) on all demographic and clinical variables except that pRBD subjects had higher rates of depression ($p<0.01$), selective-serotonin reuptake inhibitor use (SSRI; $p<0.01$), and lower language ($p=0.04$) and visuospatial ($p=0.02$) cognitive scores. Total UPDRS scores were similar in both groups; although postural scores were higher in the pRBD group, this did not reach statistical significance.

The supplementary table shows the results of the principal components analysis. Nearly 80% of the variance in gait measures was explained by three factors, with nearly equal distribution amongst the factors. Measures of rhythm (cadence, swing-, and stance-time) loaded most heavily on factor one. Measures of pace (velocity, stide length and double limb support) loaded most on factor two. Measures of stride variability loaded most on factor three. Table 2 illustrates the gait variables by group. pRBD was associated with fewer steps, increased swing time and greater gait variability with a trend towards a decrease in gait velocity as well. The Supplementary figure provides box plots of the gait variables by group.

Tables 3 and 4 show the linear regression models. Table 3 shows the effects of pRBD diagnosis on gait variables adjusting for age and sex (top rows), with additional correction for executive function (middle row) and visuospatial performance and Beck Depression

Inventory Scores (bottom row). pRBD was associated with decreased velocity and cadence. The pRBD group had a 30% increase in double support time variability, 29% increase in stride time variability and 46% greater swing time variability compared to no-pRBD group. Adjusting for executive performance had only a minor effect on the results. Results were similar adjusting for (a) Beck Depression Inventory scores, supplementary table 2, (b) visuospatial performance (not shown), or (c) all of these factors plus visuospatial performance, table 3. We found no differences when the models were adjusted for depression. However, when all variables were added there was a loss of significance for some gait parameters, and most measures of gait variability remained significant. Table 4 shows the age and sex adjusted linear regression models restricted to those with UPDRS score of ≤ 5 (N = 31 pRBD and 434 controls). Most of the reductions in cadence and increases in swing time variability associated with pRBD in the unrestricted sample remained, but the differences in pace (factor 2) lost significance. The significance of the cadence was lost (p= 0.13) when adjusting for all variables used in table 3 and limiting it to those with UPDRS ≤ 5 (not shown).

Discussion

In this cross-sectional study of a large population of community dwelling subjects without PD or dementia, those with pRBD had subtle changes in gait characterized by increased stride-to-stride variability and decreased rhythmicity and velocity. Of these differences, some, but not all, were related to subtle differences in parkinsonism, performance in executive function, measures of depression and performance in visuospatial skills. However, even in those with minimal parkinsonism on clinical examination, we observed differences in gait rhythmicity associated with pRBD. Together these findings support the hypothesis that pRBD reflects dysfunction of brainstem regions that regulate both REM-sleep and gait coordination prior to the expression of more obvious clinical features.

As disease modifying and neuroprotective treatments for synucleinopathies develop, it will be necessary to identify prodromal and pre-clinical populations. Identifying subjects with pRBD, subtle gait abnormalities, olfactory, autonomic and subtle motor dysfunction[24] may be an inexpensive and efficient way to initially screen for at-risk individuals. These simple screens, followed by secondary screening with more specific measures such as polysomnography, dopamine transporter[8] or VMAT2 [25] radioimaging, could create a highly powered group in which to test synuclein disease modifying treatments prior to significant motor or cognitive symptom onset. However, longitudinal follow up of these subjects will be required to identify the predictive power of gait abnormalities.

A unique aspect of this study is the automated assessment of subtle gait changes associated with pRBD prior to the onset of clinically significant motor and cognitive deficits. Our study complements the existing evidence that there are subtle changes in gait prior to the onset of significant motor or cognitive symptoms in a presumed synucleinopathy [24, 26]. We choose a cut-off of ≤5 for the modified UPDRS motor score to restrict the population to those with minimal motor signs in an attempt evaluate subclinical gait symptoms in the absence of otherwise clinically evident early parkinsonism. Even after excluding subjects with very mild parkinsonism, there were still gait differences in those with pRBD pointing to the utility of this method. Postuma et al [24] demonstrated that a UPDRS III motor score greater than four predicted PD spectrum disease 2 years before diagnosis with 88% sensitivity and 94% specificity, supporting our contention that the majority of the subjects in our study were free of significant motor signs leading to the gait differences.

Given the association of executive cognitive performance with gait [27–29] we included this variable in our model to further isolate the effects of pRBD. We chose not to include

measures of language as there is no clear evidence that it is associated with gait. Because of the possibility that the differences in visuospatial performance between the groups could account for differences in gait parameters we also adjusted for this and found that the results remained nearly the same. Although there was a loss of significance of a few of the variables, it should also be noted that with the colinearity of executive function, visuospatial function and depression there are limitations to these models. The underlying pathophysiology of pRBD may have contributed to the differences in cognitive function: pRBD is a risk factor for cognitive decline [11]. Although SSRI use was greater in the pRBD group we did not include it in our models as there is conflicting evidence available that this group of medications impact gait [30]. Although there is evidence that depression affects gait[31–33] when accounted for in our analyses there was no evidence that it contributed to the differences identified in pRBD subjects, supplementary table 2.

We used principle component analysis of the gait parameters to assess whether there was an association of pRBD with certain elements of the gait cycle more than others. Based on the literature, we expected an association with gait variability as well as measures of rhythm [19]. Indeed, gait elements within these components of the gait cycle remained even after adjustment for executive cognitive performance, depression and UPDRS score. Interestingly, a recent gait analysis in the MCSA group revealed a decline in gait speed of nearly 5cm/sec per decade in elderly men[17] and 4cm/sec over five years in elderly women. Likewise, the decrease in cadence identified between the groups in our study, nearly 3 steps/min, was similar to the decline seen over one decade in both men and women from a subset of this population. Thus, the diagnosis of pRBD was associated with a decline in gait speed and cadence similar to 5–10 years of age in this population.

We did not confirm RBD with polysomnography, however the MSQ is highly sensitive and specific in this population [9] . False positive classification of subjects with pRBD would be expected to attenuate the significance of our results by including those without early, probable, α- synuclein pathology. In this exploratory analysis, we did not correct for multiple comparisons and it is likely that some of our dependent variables are highly correlated. Some of our conclusions may represent type I errors. In conclusion, we identified specific motor patterns in a population of elderly subjects with pRBD without PD or cognitive impairment. If longitudinal studies reveal abnormalities in gait lead to a more rapid development of overt parkinsonism and/or cognitive impairment, they could provide support for including gait as a biomarker in RBD along with other easily obtained clinical measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic, Clinical and Cognitive Comparisons

		pRBD Median (IQR)	Controls Median (IQR)	p-value
N		42	492	-
Age		79.0 (75.3, 84.1)	79.4 (75.9, 84.0)	0.74
Sex (% Male)		81%	70%	0.14
Walking/balance/tremor problems (self report)		38.1%	31.7%	0.40
Diabetic neuropathy		7.1%	3.3%	0.18
BMI >30		23.9%	24.8%	0.89
BDI ≥13 ⟨2⟩		19.5%	5.7 %	**<0.01**
Lumbar spine disease (self report) ⟨2⟩		23.8%	19.4%	0.49
SSRI use		16.7%	4.7%	**<0.01**
UPDRS	Total (0–104)	0 (0, 5)	0 (0, 2)	0.21
	Postural (0–20)	0 (0, 2)	0 (0, 1)	0.08
MMSE*		28 (27, 28)	28 (27, 29)	0.10
Executive z-score		0.24 (−0.57, 0.81)	0.40 (−0.12, 0.97)	0.17
Language z-score		0.05 (−0.62, 0.58)	0.22 (−0.26, 0.82)	**0.04**
Memory z-score		0.32 (−0.7, 1.2)	0.43 (−0.3, 1.2)	0.21
Visuospatial z-score		0.00 (−0.66, 0.74)	0.44 (−0.19, 0.94)	**0.02**

BDI-Beck Depression Inventory;IQR – Interquartile range; IQR – Interquartile Range;

*MMSE - Mini-Mental State Examination as calculated from Kokmen Short test of Mental Status; SSRI-selective serotonin reuptake inhibitors; UPDRS-Unified Parkinson's Disease Rating Scale;

⟨N⟩Subjects missing data

Table 2

Gait Variables by pRBD cases and controls

Gait Variable	pRBD Median (range)	Controls Median (range)	p-value
Cadence (steps/min)	101.9 (62.8–130.7)	104.3 (57.6–135.9)	**<0.01**
Swing Time (per sec)	0.42 (0.26–0.55)	0.41 (0.08–0.64)	**0.01**
Stance Time (per sec)	0.76 (0.4–1.5)	0.74 (0.098)	0.06
Velocity (cm/sec)	102 (49.0–147.4)	107.1 (28.6–155.5)	0.06
Double support Time (per sec)	0.34 (0.18–0.68)	0.33 (0.20–1.00)	0.34
Stride Length (cm)	119.1 (72.8–160.9)	121.2 (56.3–168.2)	0.39
Stride Length SD (cm)	4.9 (0.7–41.5)	4.4 (0.0–48.3)	0.22
Stride Time SD (sec)	0.042 (0.01–0.48)	0.037 (0.0–1.1)	0.35
Swing Time SD (sec)	0.026 (0.01–0.37)	0.021 (0.00–0.31)	**0.02**
Stance Time SD (sec)	0.038 (0.00–0.14)	0.03 (0.0–1.1)	0.13
Double Support Time SD (sec)	0.029 (0.01–0.20)	0.025 (0.00–0.15)	**0.04**

Table 3

Linear regression estimates of association of pRBD diagnosis with gait variables

	Gait Variable		Parameter Estimate (β)	95 % Confidence Interval	p-value
1	Cadence (steps/min)	†	−4.44	−7.57 −1.31	**<0.01**
		‡	−3.89	−7.10 −0.68	**0.02**
		*	−4.04	−7.34 −0.75	**0.02**
	Swing Time (per sec)	†	0.012	−0.00 0.03	0.11
		‡	0.008	−0.01 0.02	0.27
		*	0.011	−0.00 0.03	0.15
	Stance Time (per sec)	†	0.028	−0.00 0.06	0.07
		‡	0.020	−0.01 0.05	0.20
		*	0.018	−0.01 0.05	0.25
2	Velocity (cm/sec)	†	−7.89	−13.77 −2.01	**<0.01**
		‡	−6.25	−12.07 −0.43	**0.04**
		*	−4.67	−10.56 1.22	0.12
	Double Support Time (per sec)	†	0.011	−0.01 0.04	0.39
		‡	0.006	−0.02 0.03	0.64
			0.001	−0.02 0.03	0.92
	Stride Length (cm)	†	−5.34	−10.69 0.01	**0.05**
		‡	−4.07	−9.38 1.24	0.13
		*	−2.10	−7.47 3.26	0.44
3	Stride Length SD (%)	†	15.23	−7.90 44.18	0.22
		‡	12.70	−10.54 41.97	0.31
		*	11.67	−11.95 41.62	0.36
	Stride Time SD (%)	†	29.04	2.04 63.18	**0.03**
		‡	24.97	−1.77 58.98	0.07
		*	23.16	−3.89 57.82	0.10

Gait Variable		Parameter Estimate (β)	95 % Confidence Interval	p-value
Swing Time SD (%)	†	45.70	15.25 84.19	**<0.01**
	‡	38.44	8.87 76.04	**<0.01**
	*	40.78	9.91 80.33	**<0.01**
Stance Time SD (%)	†	10.49	−13.43 41.02	0.42
	‡	6.16	−17.26 36.22	0.64
	*	4.74	−18.99 35.42	0.72
Double Support Time SD (%)	†	30.33	6.13 60.04	**0.01**
	‡	26.69	2.72 56.25	**0.03**
	*	26.62	1.99 57.20	**0.03**

† age, sex adjusted;

‡ age, gender, executive z-score adjusted;

* age, sex, executive function, Beck Depression Inventory, visuospatial function adjusted; Double support listed separately as it was nearly equally loaded in each of the three factors.

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Table 4

Linear regression estimates of pRBD diagnosis with gait variables for UPDRS scores less than 5

Gait Variable			Parameter Estimate (β)	95 % Confidence Intervals	p-value
1	Cadence (steps/min)	†	−3.99	−7.47 −0.51	**0.03**
	Swing Time (per sec)	†	0.013	−0.00 0.03	0.11
	Stance Time (per sec)	†	0.022	−0.01 0.05	0.17
2	Velocity (cm/ sec)	†	−5.00	−11.49 1.49	0.13
	Double Support Time (per sec)	†	0.006	−0.02 0.03	0.63
	Stride Length (cm)	†	−2.30	−8.16 3.56	0.44
3	Stride Length SD (%)	†	5.55	−18.87, 37.33	0.69
	Stride Time SD (%)	†	17.16	−10.75 ,53.80	0.25
	Swing Time SD (%)	†	37.35	4.95, 79.77	**0.02**
	Stance Time SD (%)	†	−1.10	−25.45, 31.20	0.94
	Double Support Time SD (%)	†	14.87	−8.99, 44.98	0.24

† age, sex adjusted