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Classifying Idiopathic Rapid Eye Movement Sleep Behavior Disorder, Controls, and Mild Parkinson's Disease Using Gait Parameters

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ABSTRACT: Background: Subtle gait changes associated with idiopathic rapid eye movement sleep behavior disorder (iRBD) could allow early detection of subjects with future synucleinopathies.

Objective: The aim of this study was to create a multiclass model, using statistical learning from prob- ability distribution of gait parameters, to distinguish between patients with iRBD, healthy control subjects (HCs), and patients with Parkinson's disease (PD).

Methods: Gait parameters were collected in 21 participants with iRBD, 21 with PD, and 21 HCs, matched for age, sex, and education level. Lasso sparse linear regression explored gait features able to classify the three groups.

Results: The final model classified iRBD from HCs and from patients with PD equally well, with 95% accuracy, 100% sensitivity, and 90% specificity.

Conclusions: Gait parameters and a pretrained statistical model can robustly distinguish participants with iRBD from HCs and patients with PD. This could be used to screen subjects with future synucleinopathies in the general population and to identify a conversion threshold to PD.

Key Words: idiopathic REM sleep behavior disorder; iRBD; gait parameters; Parkinson's disease; machine learning classification; conversion

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Robust prodromal clinical biomarkers of Parkinson's disease (PD) need to be identified to allow early interventions when dopaminergic neuronal loss is not too advanced.[1,2] Idiopathic rapid eye movement sleep behavior disorder (iRBD)[3] seems to be the strongest predictor for synucleinopathies.[4-6] It is not always pre- sent in PD, especially at the prodromal stage, but it can be used to identify other biomarkers. iRBD is associated with subtle gait abnormalities, measured in terms of clinical motor assessments.[7-10] For individualized classification, however, neither of these variables is sufficient alone, although a multiclass predictive model for iRBD, HC, and PD that uses machine learning[11,12] to combine a range of gait characteristics variability could be very useful.

Subjects and Methods

Participants

Twenty-one patients with iRBD (4 females), 21 patients with PD, and 21 healthy control subjects (HCs), matched for age, sex, and educational level, were recruited for the study. Participants with iRBD were recruited at the sleep disorders department of the Beau Soleil Clinic in Montpellier and the Regional University Hospital of Nîmes (France). iRBD was con- firmed after one-night polysomnographic recording according to the criteria of the International Classification of Sleep Disorders.[13] None of the iRBD participants had drug-induced RBD. All of them had a neurological evaluation to rule out the presence of other neurological or neurodegenerative diseases.

Patients with PD were recruited in the Department of Neurology of the Beau Soleil Clinic and the Regional University Hospital of Montpellier (France). Diagnosis was established according to the Queen Square Brain Bank criteria.[14] Participants were kept on their usual medications during the evaluation. Twelve (57%) of 21 patients with PD complained about ongoing RBD.[15] They did not have polysomnography to confirm RBD and were considered as probable RBD.

HCs were community-dwelling adults recruited via a volunteers' database maintained by the Clinical Investigation Centre of the Montpellier University Hospital.

The study was approved by the National Ethics Committee (CPP Sud Méditérannée III, Nîmes, France; ID- RCB: 2013-A01265-40). All participants gave written informed consent to participate.

Procedure

Clinical and Psychological Evaluation

Demographic characteristics and medical history were collected in a preliminary interview. Motor severity of the disease was evaluated using the Hoehn and Yahr scale[16] and Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III[17] in "on" condition. The levodopa equivalent daily dose was calculated.[18] Nonmotor and motor experiences of daily living were evaluated using MDS-UPDRS Parts I and II, respectively[17]; dysautonomia using assessment of autonomic dysfunction in PD (SCOPA- AUT)[19]; global cognitive functioning using Montreal Cognitive Assessment[20]; and anxiety and depressive symptoms using the Hospital Anxiety and Depression scale.[21]

Gait

Gait was recorded in a 20-m-long, 5-m-wide corridor. Subjects were asked to walk straight and turn around at each end of the corridor. There were three conditions: single-task walking (*ST*), dual-task walking with counting plus one (D_{+1}), and counting minus three (D_{-3}). The instruction to switch task was given each round in the middle of the corridor. Patients completed 13 rounds. Task was changed pseudorandomly. Every dual-task round was separated by a single-task round.

Six inertial measurement units (128 Hz; MobilityLab; APDM Inc., Portland, OR, USA) were strapped to wrists, ankles, and on the trunk in the sternal and lumbar position. Fifty-nine gait parameters were extracted: stride length and velocity; cadence; gait cycle time; double support; swing and stance; ranges of motion; angular velocities of legs, arms, and trunk; and asymmetries of the stride, swing, stance, leg, and arm movements.

Technical difficulties prevented recording in three subjects (PD01, HC07, and HC12).

Olfaction

Olfactory function was evaluated using standardized Sniffin' Sticks.[22]

Statistical Analyses

Group Comparisons

Independent-sample *t* test or Mann-Whitney tests were used for continuous variables, depending on the normality of the distribution, and χ^2 tests or Fisher's exact tests for categorical ones. Significance level was set at $P < 0.05$.

Classification

A classification model aggregating multiple gait features was trained to predict true health status, $y = HC,iRBD,PD$. We split the dataset into trained (75%) and test set (25%). The model learned only with the trained set, was then tested with the unseen test set, separately for each task, *ST*, D_{+1}, and D_{-3}, as well as combining the data across these tasks.

We used the probability distribution obtained for each gait measure from the repeated observations over walking rounds. Then the values of this probability in each bin were used as classification features. For a number of bins (n = 100) this resulted in an initial set of 5900 candidate features (100 bins per 59 measures).

Next, a predictive model was obtained with the well-known and easily interpretable Lasso linear regression.[23] This is a sparse learning technique that fits the true status y with the function $Y \approx f(x,b,w) = b + w_1x_1 + w_2x_2 + \ldots$, consisting of an intercept b, features x, and weights w. The weights are used to automatically select a

small subset from the highly redundant feature set through a penalizing “sifting” procedure that sets most weights to zero. The linear regression returns a continuous classification variable *Y* that is cast into the pathology class by thresholding: $\hat{y}$ =*HC* if *Y* < 1:5, $\hat{y}$ =*iRBD* if 1:5 ≤ *Y* < 2:5, and $\hat{y}$ =P*D* if *Y* ≥ 2:5 (see Fig. 1).

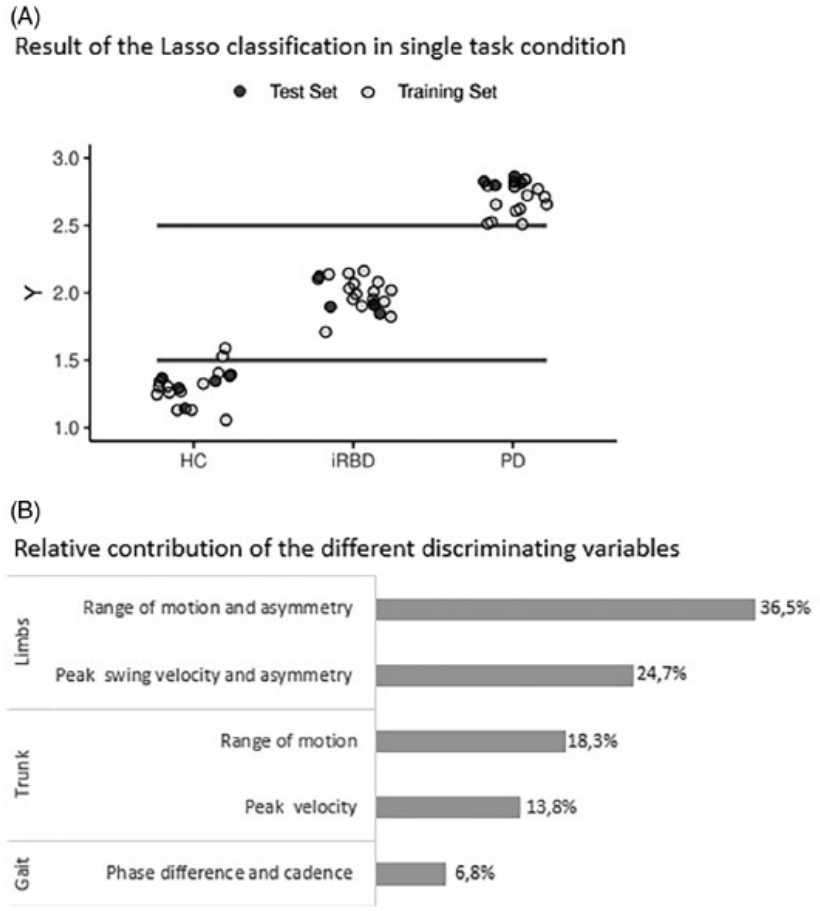

FIG. 1. Lasso classification. (A) Final model discriminating idiopathic rapid eye movement sleep behavior disorders (iRBDs) from healthy control sub- jects (HCs) and from patients with Parkinson’s disease (PD) equally well with 95% accuracy, 100% sensitivity, and 90% specificity in single task (*P* < 0.0001). (B) Contribution of the different discriminating variables. Range and speed of motion are the main contributors of the model.

Correlations with Early Markers of PD

Finally, we addressed whether the learned model agreed with known early markers of PD. To this end, we took the Pearson correlations between the aggregate classification variable *Y* from the model and clinical measures.

Results

Clinical Characteristics

Demographic and clinical characteristics for participants with iRBD, participants with PD, and HCs are presented in Table 1. Patients with PD had a mild disease with a mean Hoehn and Yahr at 1.52 ± 0.75. Dis- ease duration was 4.24 ± 2.77 years, and age at onset was 65.52 ± 7.72 years. Levodopa equivalent daily dose was 258.7 ± 214.7 mg. RBD duration was not different between patients with iRBD and patients with PD and probable RBD (11.70 ± 11.85 vs. 10.10 ± 12.22; $P = 0.8$).

In participants with iRBD, subtle motor manifestations were common, with more tremor on motor examination than HCs. They had impaired olfaction. They tended to report more dysautonomia and more depressive symptoms than HCs (Table 1). As expected, participants with iRBD had fewer motor and nonmotor, depressive, and dysautonomic symptoms than patients with PD. They did not differ for global cognition, depressive symptoms, and olfaction dysfunction (Table 1).

Classification

The accuracy of classification of iRBD from HCs and from patients with PD, as evaluated on the test set, were very high, 95% and 98%, respectively. Sensitivity of classification of iRBD from HCs and patients with PD was 100% for both, and specificity was, respectively, 91% and 95% (Fig. 1A). The same classification performance was obtained in each of the tasks (ST, D_{+1}, D_{-3}) and the combination of all three.

The Lasso method retained 34 features of 5900. For the single-task condition, these 34 features belonged to 22 gait original measures that come from six clinical signs. The contribution of these signs is reported in Fig. 1B.

We observed strong correlations (defined as coefficient of correlation > j0.6j) between the classification variable Y and most of the olfaction measures (thresh- old -0.73, $P < 0.001$; identification -0.69, $P < 0.001$; sum score -0.70, $P < 0.001$). We noted weak but significant correlations with olfaction discrimination (-0.41, $P < 0.05$), tremor (0.42, $P < 0.05$), and non-motor aspects of daily living (0.35, $P < 0.05$).

TABLE 1 . *Clinical characteristics of healthy control subjects, subjects with idiopathic rapid eye movement sleep behavior disorder, and Parkinson's disease*

Characteristics	HCs (n = 21)	iRBD (n = 21)	PD (n = 21)	*P*	
				IRBD vs. HC	IRBD vs. PD
Age (y)	69.8 ± 6.8	68.7 ± 6.9	69.8 ± 7.9	0.6	0.6
Sex (% of women)	19	19	19	1	1
Body mass index (kg/m^2)	25.8 ± 3.2	26.1 ± 3.7	25.1 ± 3.7	0.6	0.6
National adult reading test	110.2 ± 5.0	108.7 ± 9.1	111.6 ± 5.5	0.7	0.4
Education (y)	12.8 ± 4.0	12.5 ± 4.1	13.5 ± 4.1	0.8	0.3
Motor aspects					
Motor aspects of experiences of daily living (MDS-UPDRS Part II/52)	1.1 ± 1.9	0.5 ± 0.9	7.9 ± 6.4	0.3	**<0.0001**
Motor disability (MDS-UPDRS Part III/132) when treated for PD	3. 8 ± 2.6	5.3 ± 4.5	17.2 ± 9.2	0.3	**<0.0001**
Axial signs	0.6 ± 0.7	1.0 ± 0.9	2.2 ± 1.4	0.2	**<0.01**
Tremor	0.0 ± 0.0	0.7 ± 0.9	2.8 ± 2.6	**<0.01**	**<0.001**
Falls self-efficacy scale score	7.4 ± 0.9	7.5 ± 1.0	10.2 ± 4.4	0.3	**0.01**
Nonmotor aspects of daily living					
MDS-UPDRS Part I/52	4.2 ± 3.9	6.8 ± 4.9	12.2 ± 5.0	0.06	**<0.0001**
Global cognitive function (MoCA)	27.2 ± 2.1	26.2 ± 3.3	26.6 ± 2.4	0.7	0.9
Hospital anxiety depression scale: anxiety	4.4 ± 3.3	5.6 ± 3.6	6.8 ± 3.5	0.3	0.1
Hospital anxiety depression scale: depression	1.9 ± 2.6	3.1 ± 2.4	4.9 ± 3.5	0.06	**0.03**
Dysautonomia (SCOPA-AUT)	5.4 ± 2.9	7.7 ± 5.2	13.6 ± 5.7	0.07	**<0.001**
Olfaction					
Threshold	7.4 ± 1.7	3.2 ± 2.1	3.7 ± 1.5	**<0.0001**	0.6
Discrimination	11.4 ± 2.0	8.6 ± 3.2	7.8 ± 3.4	0.001	0.4
Identification	13.1 ± 1.6.2	7.6 ± 3	6.8 ± 3.6	**<0.0001**	0.3
Sum score	31.9 ± 3.4	19.4 ± 7.1	18.2 ± 7.0	**<0.0001**	0.5

Data are shown as mean ± SD. Boldface values reached statistical significance of $P < 0.05$.
HC, healthy control subject; iRBD, idiopathic rapid eye movement sleep behavior disorder; PD, Parkinson's disease; MoCA, Montreal Cognitive Assessment; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SCOPA-AUT, assessment of autonomic dysfunction in Parkinson's disease.

Discussion

We have demonstrated that using statistical learning methods to explore gait measures, one can identify robust discriminating variables to screen HCs from patients with high risk to develop synucleinopathies (mostly PD or dementia with Lewy bodies), such as patients with iRBD. Thanks to a noninvasive, quick-to- perform, and cheap gait detection method, we can screen future synucleinopathies from HCs. We observed that using a dual task did not improve our accuracy, making the testing duration even faster.

Our discriminating variables are strongly correlated with olfaction dysfunction, which is another marker associated with high risk for future synucleinopathies. Our method, which also allows discriminating patients with iRBD and PD, could help address the challenging task of distinguishing early PD and advanced iRBD.

Subtle gait disorders have already been identified as risk factors for future PD.[7-10] However, these differences were identified at the group level but never did authorize a screening of a future PD population. Recent studies examined the role of gait in conversion to PD.[24,25] Our approach confirms their results but also differs from theirs because it quantifies the role of gait features into a predicting statistical model.

A large set of gait parameters was collected and analyzed, as well as their variability within time. This last subset of variables contributed to the sensitivity of group screening. Based on the variability of the distribution of our data, we successfully screened iRBD from HCs and patients with PD with a sensitivity of 100% and a specificity of 90% with very high levels of significance.

Our results confirm that gait disorders occur early in the development of synucleinopathies. The gait parameters that classified our groups were mostly amplitude and speed of movement. These abnormalities are the classical clinical signs observed in a full-blown parkinsonian syndrome but are so subtle in iRBD that they usually remain undetectable for clinicians. It is their variation in time that allowed us to screen subjects with iRBD, with high risk to develop synucleinopathies, compared with HCs and patients with PD. Gait parameters of patients with iRBD appear to exhibit parkinsonian signs, but in a discreet, discontinuous, and variable way. Cadence and phase difference were also involved, suggesting a rhythmicity dysfunction. This is in line with our recent results suggesting rhythm disturbances as a potential early marker of PD.[26]

The main limitations of our study are the low sample size and the cross-sectional rather than longitudinal design of the study, which calls for further investigation in a larger population and in a longitudinal way. We could also have used more challenging dual tasks.

In conclusion, our work supports the idea that subtle and time-varying gait disorders appear early in PD or more broadly in synucleinopathies even at the

preclinical phase of the disease. Our results encourage considering the use of new technologies to measure gait parameters and their time variability as screening tools in studies targeting disease-modifying agents. This approach is also a promising tool for the prediction of disease progression at a prodromal stage.

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Data Availability Statement

Data are available on request

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