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Prediagnostic markers of idiopathic Parkinson's disease: Gait, visuospatial ability and executive function

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ABSTRACT

Background: Idiopathic Parkinson's disease (IPD) has a long preclinical phase.
Research question: This study assesses data on prediagnostic markers of IPD from a longitudinal, natural history study of aging.
Methods: Participants were selected from the database of the Baltimore Longitudinal Study of Aging, and included 10 prediagnosed IPD cases (eight men and two women) and 30 age and sex matched healthy controls. Patients with prediagnosed IPD had already had an assessment for IPD 2.6 ± 1.3 years (range 1.0–5.3 years) before the actual diagnosis, including: gait speed (six-meter corridor walk), spatio-temporal gait parameters using Vicon motion capture, balance, upper-limb motor skills, neuropsychological profile, and non-motor symptoms.
Results: Prediagnosed IPD cases compared to controls had slower gait speed (Δ=-0.13 m.s^{-1}, p = 0.03) due to shorter step length (Δ= −5 cm, p = 0.004), worse visuospatial ability (card rotation test, Δ=-42, p = 0.0001) and worse executive function (category fluency test, Δ=-2.6, p = 0.04).
Significance: Our findings identify dimensions that merit further study as prediagnostic markers of Idiopathic Parkinson's disease to identify patients who might benefit from future neuroprotective therapy in order to delay, or prevent, clinical manifestations.

1. Introduction

Idiopathic Parkinson's disease (IPD) is a neurodegenerative disorder characterized by motor symptoms. These symptoms are due to loss of dopaminergic nigrostriatal neurons, and occur only when 70–80% of striatal dopamine is depleted, corresponding to about 50% cell death [1]. There is a long prodromal period, the neuropathological process beginning about 5 years before the onset of motor symptoms. Identifying individuals during this period could be of great utility for future trials of neuroprotective therapies, which might prevent the degeneration of the dopaminergic neurons [2]. Consequently, efforts are needed to identify appropriate early markers of IPD.

IPD also causes non-motor symptoms from early to advanced stages of the disease, including: impaired olfaction, depression, autonomic dysfunction, and cognitive impairment. Moreover, there is a large body of evidence that non-motor symptoms can precede the diagnosis of IPD by several years [3] during the prodromal phase of IPD: constipation, orthostatic hypotension, erectile dysfunction, urinary dysfunction, impaired olfaction, rapid eye movement sleep behavior disorder [4], sleepiness, anxiety, and depression [5]. There are also some gait changes in the advanced stage of IPD, which are already present in early stages [6,7], before any visible gait disturbances, such as decreased gait speed and increased stride-to-stride variability. However this evidence comes largely from retrospective studies after diagnosis, or from studies of special high-risk populations such as asymptomatic LRRK2 (Leucine-rich repeat kinase 2) mutation carriers [8–10] or patients with idiopathic rapid eye movement sleep behavior disorder (IRBD) [11–14]. As yet there has been no evidence of markers during the prodromal phase of IPD from populations experiencing natural aging, in whom over 90% of IPD cases occur.

Based on data from a long-standing study of human aging across the adult lifespan (the Baltimore Longitudinal Study of Aging, BLSA), we identified IPD cases and controls and evaluated evidence years prior to diagnosis. We sought to determine i) whether and which subtle gait

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disorders precede the diagnosis of IPD, and ii) other prodromal markers.

2. Methods

2.1. Study design and setting

The BLSA is a study of human aging across the adult life span, conducted by the National Institute on Aging (NIA) Intramural Research Program. The BLSA continuously enrolls healthy volunteers aged 20 years and older who are followed for life regardless of the development of age-related diseases. Participants undergo three days of testing at the NIA Clinical Research Unit in Baltimore at intervals of four years before age 60 years, two years between 60 and 79 years, and one year after 80 years. The present sub-study of the BLSA has been approved by the Institutional Review Board, and all participants have signed informed consent.

2.2. Participants

The sample consisted of 40 participants (10 prediagnosed cases of IPD and 30 healthy controls), $\geq$ 70 years, who had their first visit between January 13th, 1960 and June 14th, 2015, and were followed for an average of 21 years (range 0–55.5 years). As IPD diagnosis was not clearly indicated in the BLSA database, participants who developed IPD during their follow-up were identified from the BLSA database based on the most relevant existing criteria: i) the medical history interview ("Has a doctor ever told you that you had Parkinson's disease?"), ii) prescribed medications (levodopa, dopamine receptor agonists, etc.), and iii) disease status after the physical examination (parkinsonian syndrome). From the BLSA database, 95 participants met at least one criterion. Subsequently, we reviewed the medical chart of each participant to ensure that the participant: i) met prospective positive criteria for IPD during the next BLSA visits according to the UK brain bank criteria and ii) did not meet exclusion criteria for IPD. The time of IPD diagnosis was defined as the first BLSA visit with the presence of at least one of these three criteria. Since the primary goal of the study was to evaluate subtle gait disturbances during the prediagnostic phase of IPD, we only selected participants who had completed gait assessments prior to the visit for IPD diagnosis. There were 10 prediagnosed IPD cases which met all requirements (Fig. 1). These 10 participants were followed for an average of 2.6 ± 1.3 years (range 1.0–5.3 years) before diagnosis. Thirty healthy controls were matched to the 10 prediagnosed cases of IPD for age, gender, height, and weight.

2.3. Measurements

2.3.1. Gait assessment

Gait assessment consisted of: i) a 6-meter corridor walk, ii) a 400-meter corridor walk, iii) an instrumental gait analysis for spatio-temporal and temporophasic parameters (Supplementary Table 1), and iv) an interview on falls and fear of falling.

2.3.2. Balance assessment

Balance assessment consisted of: i) a semi-tandem stand task, ii) a tandem stand task, iii) a one-leg task, and iv) an interview.

2.3.3. Upper-limb motor assessment

Upper-limb motor assessment included: i) a hand rapid alternating movement test, ii) a finger tapping test, and iii) a Purdue pegboard test.

2.3.4. Neuropsychological assessment

The following tests were used: the Mini-Mental State Examination, verbal fluency tests, the Benton visual retention test, the California verbal learning test, the digit symbol substitution test, the digit span test, the Trail-Making Test, the card rotation test, and the Boston naming task.

2.3.5. Non-motor symptoms assessment

Orthostatic hypotension.

Depression. The 20-item Center for Epidemiologic Studies Depression Scale (CESD).

Sleep disorders. The 5-item Women's Health Initiative Insomnia Rating Scale (WHIIRS).

Urinary symptoms. The 7-item American Urological Association Symptom Score (AUASS).

2.4. Statistical analysis

A Mann-Whitney test was used to compare the medians of quantitative variables between groups. A Fisher's exact test was used to compare the medians of nominal (categorical) variables between groups. For all variables significantly different between both groups, a Spearman rank correlation was used to investigate their relatedness. Statistical analyses were performed using Statgraphics Centurion (Statpoint Technologies, Inc).

3. Results

The prediagnosed IPD cases and controls were similar in terms of demographic characteristics, conditions potentially affecting gait, and neurological disorders (Table 1).

3.1. Clinical gait and balance assessment

Compared to controls, prediagnosed IPD cases walked more slowly in the usual gait speed condition of the 6-meter walk test (Δ = 0.08 m.s^{-1}, p = 0.01), but not in the maximal gait speed condition. They also tended to walk more slowly in the 400-meter walk test (Δ = 0.13 m.s^{-1}, p = 0.07). There were no significant group differences in time variation (Table 2). Height adjustment did not change the results. No significant differences were found between groups for stance tasks (i.e., semi-tandem stand, tandem stand, and one-leg stand) (Supplementary Table S2). Half of the prediagnosed IPD cases reported impaired balance when walking compared to 20% of controls (p = 0.03). Half of the prediagnosed IPD cases reported impaired balance with closed eyes versus 43% among controls (p = 0.22) (Supplementary Table S2). Two thirds of the prediagnosed IPD cases reported a fall in the past year compared to 15% of controls (p = 0.07). One prediagnosed IPD case reported a fear of falling versus 3 among controls (p = 0.44) (Table 2).

No significant differences were found between groups for upper-limb motor tasks (Supplementary Table S3).

3.2. Instrumental gait assessment

In the usual speed condition, compared to controls, prediagnosed IPD cases had slower gait speed (Δ = -0.13 m.s^{-1}, p = 0.03) due to shorter step length (Δ = −5 cm, p = 0.004) and stride length (Δ = −11 cm, p = 0.006). No significant differences were found between groups for the other domains of gait (i.e., rhythm, phases, and base of support) (Table 3).

In the maximal gait speed condition, compared to controls, prediagnosed IPD cases had shorter step length (Δ = −8 cm, p = 0.04) and stride length (Δ = −14 cm, p = 0.03), despite no statistically significant difference between groups in gait speed (Δ = -0.13 m.s^{-1}, p = 0.33). No significant differences were found between groups for the other domains of gait (i.e., rhythm, phases, and base of support) (Table 3).

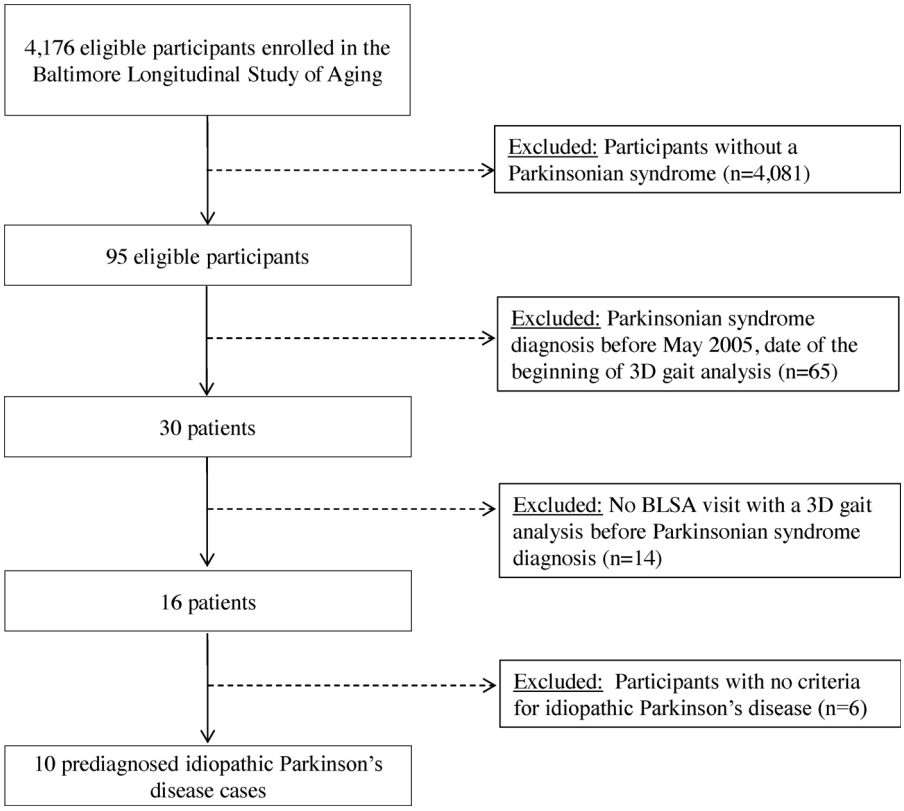

Fig. 1. Flowchart describing the selection of the study participants.

Table 1
Demographic characteristics and comorbidities of the study sample.

	Prediagnosed Parkinson's disease	Controls	p-value
Demographic characteristics			
Age (years)	79.4 (72.8-86.3)	79.5 (72.8-91.3)	0.92
Gender (Male/Female)	8/2	24/6	0.66
Height (m)	1.75 (1.63-1.84)	1.74 (1.53-1.90)	0.81
Weight (kg)	80.2 (66.5-95.8)	76.3 (55.7-114.1)	0.51
Body mass index (kg/m^2)	25.8 (21.3-33.1)	26.1 (19.1-36.4)	0.86
Gait-disturbing conditions			
Pain when walking	0	5	0.21
Vision			
Excellent	4	8	0.34
Good	5	20	0.28
Fair	1	2	0.44
Poor	0	0	–
Very poor	0	0	–
Heart failure	0	0	–
Chronic bronchitis	0	2	0.55
Neurological conditions			
Dementia	0	0	–
Neuropathy	1	2	0.44
Stroke	0	0	–
Transient ischemic attack	0	1	0.75
Spinal stenosis	2	2	0.21

Median (min-max) values are reported for demographic characteristics, and the number of subjects is reported for variables related to gait-disturbing or neurological conditions.

Table 2
Results of clinical gait assessment.

	Prediagnosed idiopathic Parkinson's disease	Controls	p-value
Corridor walk performance			
6-meter corridor walk			
Usual gait speed ($m.s^{-1}$)	0.97 (0.71-1.15)	1.05 (0.76-1.40)	**0.01**
Maximal gait speed ($m.s^{-1}$)	1.41 (1.01-2.23)	1.57 (1.10-2.10)	0.22
400-meter corridor walk			
Gait speed ($m.s^{-1}$)	1.26 (0.92-1.77)	1.39 (0.93-1.91)	0.07
Mean lap time (s)	31.8 (22.6-43.7)	28.9 (21.0-43.0)	0.07
Lap time variation (SD)	0.72 (0.44-1.6)	0.84 (0.34-1.91)	0.97
Risk for falls			
Falls in the last year			
No fall	6	26	0.07
1 fall	4	4	0.07
2-3 falls	0	0	–
4-5 falls	0	0	–
≥ 6 falls	0	0	–
Fear of falling			
Never	9	27	0.44
Rarely	1	1	0.38
Some of the time	0	2	0.55
Most of the time	0	0	–
All the time	0	0	–

Median (min-max) values are reported for gait variables, and the number of subjects is reported for variables related to risk of falls.

Table 3
Results of instrumental gait assessment in usual gait speed condition, after adjustment for possible confounding variables.

Parameter	Usual gait speed			Maximal gait speed		
	Prediagnosed Parkinson's disease	Controls	p-value	Prediagnosed Parkinson's disease	Controls	p-value
Rhythm						
Cadence (steps. min^{-1})	110 (102-120)	111 (91-132)	0.92	134 (111-159)	132 (113-162)	0.81
Step time (s)	0.55 (0.50-0.59)	0.54 (0.46-0.66)	0.98	0.45 (0.38-0.54)	0.45 (0.37-0.53)	0.86
Stride time (s)	1.09 (1.00-1.17)	1.09 (0.92-1.32)	0.93	0.90 (0.76-1.08)	0.91 (0.74-1.06)	0.84
Swing time (s)	0.40 (0.38-0.44)	0.41 (0.36-0.52)	0.27	0.35 (0.32-0.40)	0.36 (0.30-0.42)	0.68
Stance time (s)	0.70 (0.62-0.75)	0.68 (0.56-0.81)	0.67	0.55 (0.44-0.70)	0.56 (0.44-0.66)	0.84
Single support time (s)	0.40 (0.38-0.44)	0.41 (0.36-0.53)	0.30	0.35 (0.32-0.40)	0.36 (0.30-0.42)	0.68
Phases						
Swing (% GC)	37.0 (33.7-38.5)	37.6 (35.6-40.4)	0.16	39.4 (35.0-41.9)	39.3 (37.0-42.7)	0.73
Stance (% GC)	63.0 (61.5-66.3)	62.4 (59.6-64.4)	0.16	60.6 (58.1-65.0)	60.7 (57.3-63.0)	0.73
Single support (% GC)	36.9 (34.0-38.5)	37.8 (35.3-40.3)	0.07	39.2 (34.8-42.2)	39.2 (36.9-43.3)	0.77
Double support (% GC)	26.0 (23.0-32.3)	24.6 (19.3-29.1)	0.09	21.4 (15.9-30.2)	21.6 (14.1-26.1)	0.78
Double support time (s)	0.30 (0.24-0.37)	0.27 (0.20-0.33)	0.19	0.19 (0.12-0.33)	0.20 (0.11-0.27)	0.81
Pace						
Gait speed ($m.s^{-1}$) [1]	0.60 (0.33-0.69)	0.65 (0.41-0.85)	**0.03**	0.83 (0.61-1.04)	0.86 (0.56-1.21)	0.21
Step length (cm) [1]	34 (18-36)	36 (22-46)	**0.003**	39 (33-42)	42 (26-52)	**0.03**
Stride length (cm) [1]	67 (34-72)	72 (44-91)	**0.003**	77 (65-84)	83 (51-105)	**0.04**
Base of support						
Step width (cm) [2]	0.03 (0.02-0.04)	0.03 (0.01-0.06)	0.23	0.03 (0.02-0.03)	0.03 (0.02-0.06)	0.15

Median (min-max) values of these parameters are reported after adjustment for: [1] height, and [2] inter-anterior superior iliac spinous distance. The p-value indicates if there is a significant difference between groups.

3.3. Non-motor symptom assessment

There were no significant differences between prediagnosed IPD cases and controls in orthostatic hypotension, depression, sleep disorders, or urinary symptoms (Supplementary Table S4).

3.4. Neuropsychological assessment

Compared to controls, prediagnosed IPD cases had worse performances in both the card rotation test ($\Delta = 42$ number classified correctly minus the number classified incorrectly, $p < 0.001$) and the category fluency test ($\Delta = 2.6$ items, $p = 0.04$). No significant differences were found between groups for the other tests (Table 4).

3.5. Correlations between gait parameters and neuropsychological scores

In the usual gait speed condition, both gait speed and step length were correlated with the card rotation test ($r = 0.43$, $p = 0.008$) and the category fluency test ($r = 0.41$, $p = 0.009$). In the maximal gait speed condition, both gait speed and step length were correlated with the category fluency test ($r = 0.47$, $p = 0.003$) (Supplementary Table S5).

4. Discussion

To our knowledge, this is the first report of markers during the prediagnostic phase of typical IPD. The main findings of the study are 1) subtle gait disturbances including i) decreased step length and gait speed at usual gait speed, and ii) decreased step length at maximal gait speed and 2) non-motor findings including altered visual spatial ability and decreased executive function.

Prior studies have focused on high-risk populations such as asymptomatic LRRK2 mutation carriers [8] or patients with IRBD [11–14], in whom the prodromal phase may differ compared to IPD [2]. Because the BLSA is a large prospective natural history study with multiple assessments of markers relevant to prodromal IPD, we were able to use data from visits prior to the actual diagnosis of IPD to assess manifestations during the prediagnostic phase.

4.1. Prediagnostic gait markers of idiopathic Parkinson's disease

At usual gait speed, prediagnosed IPD patients showed slower gait speed, as quantified by both clinical and instrumental assessments. This result has been previously reported in IRBD patients [12–14]. Slower gait speed (i.e., bradykinesia-slowed movement) resulted from the inability of prediagnosed IPD patients to generate sufficient stride (or step) length (i.e., gait hypokinesia-reduced movement amplitude) [15–17]. This result is consistent with the findings of Morris et al. who reported that IPD patients have particular difficulty with the internal regulation of stride length [15], even though cadence control (steps per minute) remains intact [16]. The reason for reduced stride length has not yet been fully elucidated, although it has been suggested that gait

Table 4
Results of neuropsychological assessment.

	Prediagnosed idiopathic Parkinson's disease	Controls	p-value
Mini-Mental State Examination	28.5 (27-30)	29.0 (22-30)	0.50
Card Rotation Test	49 (25-67)	91 (44-160)	**0.0001**
Benton Visual Retention Test	9.0 (3-12)	7.5 (1-26)	0.78
CVLT, immediate free recall	46 (29-57)	50 (21-80)	0.31
CVLT, short-delay free recall	9.5 (4-13)	9.0 (0-16)	0.46
CVLT, long-delay free recall	9 (4-15)	11 (0-16)	0.22
Letter Fluency Test	12.2 (7.0-18.3)	14.5 (5.3-24.3)	0.17
Category Fluency Test	11.7 (6.3-17.0)	14.3 (7.0-21.0)	**0.04**
Boston Naming Test	55 (37-60)	57 (14-60)	0.13
Digit Span Test Forward	8.5 (6-13)	7.5 (4-13)	0.26
Digit Span Test Backward	7.5 (4-13)	6.0 (3-12)	0.36
Digit Symbol Substitution Test	33.5 (23-49)	38.0 (17-58)	0.32
Trail Making Test, Part A	41.5 (24-66)	31.0 (18-63)	0.11
Trail Making Test, Part B	86.5 (52-212)	71.5 (33-225)	0.26

Median (min-max) values are reported.
CVLT: California Verbal Learning Test.

hypokinesia could reflect a difficulty in activating the locomotor control system (i.e., inadequate contribution to cortical motor set by the basal ganglia). This hypothesis is based on the finding that normal stride length can be elicited in IPD patients using either attentional strategies or visual cues, possibly because both of these methods require patients to focus their attention on walking with the sole criterion of stride length [17]. In contrast, the performance of a concurrent cognitive task while walking (i.e., dual tasking) would likely amplify the inability of prediagnosed IPD patients to generate appropriate stride length, all the more pronounced with increasing cognitive load [18]. Of note, in some studies, slower gait speed was not found in IRBD patients [11], nor in asymptomatic LRRK2 mutation carriers [8]. These contradictory results could be explained because i) IRBD patients and asymptomatic LRRK2 mutations carriers may enter the preclinical phase earlier than our prediagnosed IPD patients, ii) all IRBD patients and asymptomatic LRRK2 mutations carriers did not develop Parkinson's disease and iii) genetic Parkinson's disease and IRBD-converted Parkinson's disease may not have the same preclinical gait pattern as IPD.

At maximal gait speed, our prediagnosed IPD patients were not limited in the maximum speed they could achieve, as shown by the percentage increase in speed between the usual and maximal gait speed conditions (median: 137.4% for controls and 137.5% for prediagnosed IPD patients). This finding is consistent with the hypothesis put forth by Mazzoni et al. (2012) suggesting that the core abnormality in bradykinesia should be described as a speed selection problem [19], and not as the loss of the ability to move at normal speeds [20]. Besides, the effect size for gait speed under maximal gait speed condition (η^2 = -0.18, small effect) was smaller than that observed under usual gait speed condition (η^2 = -0.35, moderate effect). Yet interestingly, at maximal gait speed, our with prediagnosed IPD patients still showed shorter stride length compared to controls. The effect sizes for step length under maximal gait speed condition (η^2 = -0.33, moderate effect) were similar to those observed under usual gait speed condition (η^2 = -0.44, moderate effect). Hence, one of the key manifestations of a gait disorder in prediagnosed IPD patients was the inability to generate sufficient stride length [15–17].

4.2. Other prediagnostic markers of idiopathic Parkinson's disease

The secondary result of our study is that there were higher-order cognitive deficits in prediagnosed IPD patients, notably in visuospatial ability and executive function. We did not find any upper-limb motor impairments or non-motor symptoms.

In our study, prediagnosed IPD patients had a deficit in visuospatial ability. This deficit was previously found in the early stages of IPD [21] and IRBD patients [12]. Other deficits in visuomotor control [22], visuospatial memory and learning [23] have been reported in the early stages of IPD. Yet interestingly, the recent study of Chahine et al. found preserved visuospatial skills in healthy adults with hyposmia and dopamine transporter binding reduction [24]. In our study, several tests evaluated visuospatial abilities: i) the Mini-Mental State Examination with one of the 30 items, which assesses visual constructive ability, ii) the Benton Visual Retention Test, which assesses visual perception and visual memory, and iii) the Card Rotation Test, which assesses visuospatial rotation ability. Only performance on the latter test was lower in prediagnostic PD patients compared to controls, suggesting that mental rotation is predominantly altered among visuospatial abilities in those patients.

Our prediagnosed IPD patients also had a decreased performance of category fluency, which may reflect impairment in executive function. Altered performance of category fluency was previously reported in early stage IPD [21], but also in healthy adults with hyposmia and dopamine transporter binding reduction [24], which is not specific to IPD but all atypical parkinsonian syndromes. Nevertheless, results were different for category and letter fluency. Differentially worse performance on category versus letter fluency suggests greater semantic versus retrieval difficulties [25,26].

In contrast, prediagnosed IPD patients had preserved mental status (MMSE), similar to asymptomatic LRRK2 mutation carriers [8] and IRBD patients [12]. However, authors found that healthy adults with hyposmia and dopamine transporter binding reduction had lower global cognitive function [24]. These contradictory results could be due to our IPD-specific population compared to their atypical parkinsonian syndrome population. Patients with LRRK2-related Parkinson's disease demonstrated better cognitive performance [27,28]. Moreover, in our study, several cognitive functions (visuospatial ability and executive function) were found to be correlated with gait speed and step length, suggesting a common underlying condition.

Prediagnosed IPD patients had preserved upper-limb motor performance. This differs from the impaired performance found in IRBD patients [13,14]. However, 56 to 78% of these IRBD patients had Parkinsonism, with a lower UPDRS (Unified Parkinson's Disease Rating Scale) score compared with controls. Subtle motor changes may precede diagnosis of Parkinson's disease, and the risk of Parkinson's disease clearly increases with higher UPDRS scores. Our results suggest that gait changes may precede other motor changes in prediagnosed IPD patients, reflecting that gait is not a simple motor task among all motor tasks, but is more integrative, reflecting general health [29].

Finally, as found in previous studies, our prediagnosed IPD patients had no orthostatic hypotension [8,14], no depression [8,14], no sleep disturbances [8], and no urinary symptoms [8]. In contrast, the IRBD

patients in the study of Postuma reported urinary symptoms, not surprisingly considering that IRBD patients may convert to either Parkinson's disease or an atypical parkinsonian syndrome, known as multiple system atrophy. In the latter, urinary symptoms emerge early and precede motor symptoms by several years [30,31].

Motor findings are predicted to occur after non-motor symptoms in IPD, as the earliest neuropathological abnormalities in Parkinson's disease are outside the motor system [32]. Effectively, Braak (2003) described widespread areas of neurodegeneration in Parkinson's disease, and suggested that degeneration of the olfactory and lower brainstem structure (e.g., dorsal motor nucleus of the vagus) occurred before that of the susbtantia nigra [33]. Nevertheless, some important structures involved in gait control are located in the brainstem (e.g., the pedonculopontine nucleus), below the substantia nigra, and could be altered before the manifestation of classical motor symptoms [34].

Our study has significant strengths and some limitations. Major strengths include our focus on the most common and classic forms of IPD, which occur especially with increasing age. Due to the systematic longitudinal prospective nature of the BLSA, we were able to capture performance and symptoms years prior to the actual diagnosis of IPD. Thus for the first time, we provide evidence of preclinical manifestations of the disease in its most widespread form. We were able to capture data on multiple potential markers including detailed gait and cognitive assessment as well as other factors. Our study also has limitations. Since IPD is not common (the incidence at age 50–59 years is 107 per 100 000 and increases to 1087 at age 70–79 years) [35], our sample size of IPD patients is modest. Since the BLSA is a study of the adult lifespan, it does not focus on specific diseases and thus lacks disease-specific scales such as the UPDRS.

In conclusion, we found that changes in gait and cognition were present during the prediagnostic phase of IPD and may occur earlier than classical non-motor symptoms. Further studies are needed to corroborate these results. If they are confirmed, these changes might serve as markers to improve the early detection of IPD patients, who could then benefit from pharmacological neuroprotection trials and/or prevention trials of lifestyle-related interventions in order to delay, or even prevent, clinical manifestations.

Conflict of interest

The authors declare no competing financial interests.

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