Neurophysiologie Clinique/Clinical Neurophysiology (2019) 49, 173—180

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COMPREHENSIVE REVIEW

Posturo-locomotor markers of preclinical Parkinson's disease

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Received 28 December 2018; accepted 2 January 2019
Available online 25 January 2019

KEYWORDS
Gait and balance disorders;
Parkinson's disease;
Preclinical;
Prodromal;
Presymptomatic

Summary Parkinson's disease (PD) is known to have a long prodromal stage due to the degeneration of dopaminergic neurons of the substantia nigra pars compacta over the course of many years without clinical manifestations of PD. When the diagnosis is made, the neuropathological process is already well entrenched. Consequently, identifying individuals during this prodromal period could be very helpful for future trials of neuroprotective or disease-modifying therapies, which might slow or prevent the degeneration of dopaminergic neurons. Thus, efforts are needed to determine appropriate early markers of PD. Gait and balance disorders are frequent during the early stages of PD. This systematic review aims to determine if gait and balance disorders occur before the diagnosis of PD and if so, whether they could be used as markers of preclinical PD. Findings reveal that, at the presymptomatic stage of PD, impaired basal ganglia function leads to disorders in gait and balance. Both clinical and instrumental assessments allow early detection of these disorders, particularly when performed under challenging conditions (e.g. dual-task). Among all studied parameters, temporal gait variability and arm kinematics appear to be promising markers of preclinical PD.

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by classic motor symptoms (i.e., bradykinesia, rigidity, tremor, and postural instability). These motor symptoms are due to loss of dopaminergic nigrostriatal neurons from the substantia nigra pars compacta (SNpc), and only arise after a 70—80% reduction of striatal dopamine, which corresponds to 50% cell death of dopaminergic neurons of the SNpc [34]. There is growing evidence that PD is characterized by a long prodromal period, the neuropathological process beginning about 5 years before the onset of motor symptoms [10]. Identifying individuals during this period could be of great utility for

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https://doi.org/10.1016/j.neucli.2019.01.001
0987-7053/

future trials of neuroprotective therapies, which might prevent the degeneration of the dopaminergic neurons [25,31]. Indeed, when a patient becomes symptomatic, the neuropathological process is already well entrenched. Potential neuroprotective and disease-modifying therapies in the prediagnostic phase may slow or halt irreversible progressive neurodegeneration, and consequently could delay or prevent the clinical symptoms. Hence, efforts are needed to identify robust early markers of preclinical PD. Several studies have focused on detecting PD symptoms in the prodromal phase using a variety of nonmotor biological markers (e.g., olfaction, autonomic dysfunction, sleep disorders, and transcranial sonography of the SNpc). Because PD diagnosis is still largely based on its motor features, it is reasonable to speculate that subtle changes in motor function will be present prior to the appearance of the cardinal motor signs required for diagnosis. The goal of this review is to describe existing posturo-locomotor markers of preclinical PD.

Methods

Literature search

The bibliographical search consisted of a literature review through October 2018 using the PubMed database as well as the references cited in the selected articles. Studies were considered eligible if:

- the data were related to gait and balance disorders;
- the patients were diagnosed with Parkinson's disease prospectively and/or retrospectively;
- the data were collected at a preclinical stage.

The search terms included:

- gait OR locomotion OR walking OR balance OR posture OR postural balance OR postural equilibrium OR accelerometry OR kinematics OR posturography;
- Parkinson's disease OR parkinsonian syndrome OR REM sleep behavior disorder;
- presymptomatic OR asymptomatic OR prodromal OR biomarker OR preclinical OR premanifest.

All studies needed to be written in English and to report original data (no review) and human research (no animal research).

Selection of studies

After the initial search, all articles were first screened based on their title and abstract. Articles which the two authors (NC and LMD) agreed to be eligible were included. Overall, among the 175 articles initially identified, 140 were excluded based on their title, and 28 were excluded based on their abstract for at least one of the following reasons:

- no clinical or instrumental assessment of gait and balance; data not collected at the preclinical stage of the disease (e.g., Parkinson's disease de novo).

To the remaining seven eligible studies, another four studies were added: three studies extracted from references cited in the seven selected articles and our in press article. Thus, this systematic review included 11 studies (Fig. 1).

Analysis

For each study, the following data were extracted: population characteristics, description of gait and balance assessments (i.e., types of assessment, tasks and studied parameters), and a summary of findings. No meta-analysis was carried out due to the limited number of studies available and the diversity of data (e.g., gait and balance parameters, preclinical population etc.).

Results

Eleven articles were selected for this review, including ten cross-sectional studies [6,7,9,18,21,22,24,26,27,36] and one longitudinal study [30]. They are summarized in Table 1. The studied populations were diverse:

- one study included patients with sporadic idiopathic PD [6];
- four studies included patients with genetic PD, of which three included *LRRK2* gene mutation carriers [22,24,36] and one included *PINK1* gene mutation carriers [26];
- six studies included patients with increased risk of PD, of which five included patients with rapid eye movement (REM) sleep behavior disorder [7,9,21,27,30] and one included patients with high-risk PD [18].

High-risk PD was defined as the presence of an enlarged area of hyperechogenicity of the substantia nigra and the presence of one of the cardinal symptoms of PD [i.e., bradykinesia or rigidity as assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) — Motor examination]. In all studies, patients were compared with age-matched healthy controls. For genetic PD, the control group comprised healthy relatives who were non-carriers of the mutation gene in two studies [22,24] and unrelated controls in two studies [26,36]. Assessments concerned gait in eight studies [9,21,22,24,26,27,30,36], balance in two studies [7,18], and both gait and balance in one study [6]. Clinical assessments of gait and balance were performed in three studies [9,27,30], instrumental assessments in seven studies [7,18,21,22,24,26,36], and both clinical and instrumental assessments in one study [6].

Discussion

Impaired basal ganglia function in patients with PD leads to disorders in gait and balance. Changes in gait are obvious in the advanced stage of PD [4,12], but they are already present in the early stages [2,11], even before any visible or symptomatic gait disturbances, such as decreased gait speed and increased stride-to-stride variability. Likewise, changes in balance are prominent in the advanced stage of PD, as reflected by the Hoehn & Yahr scale, where postural instability is represented only in the advanced stages 3 to 5 [16].

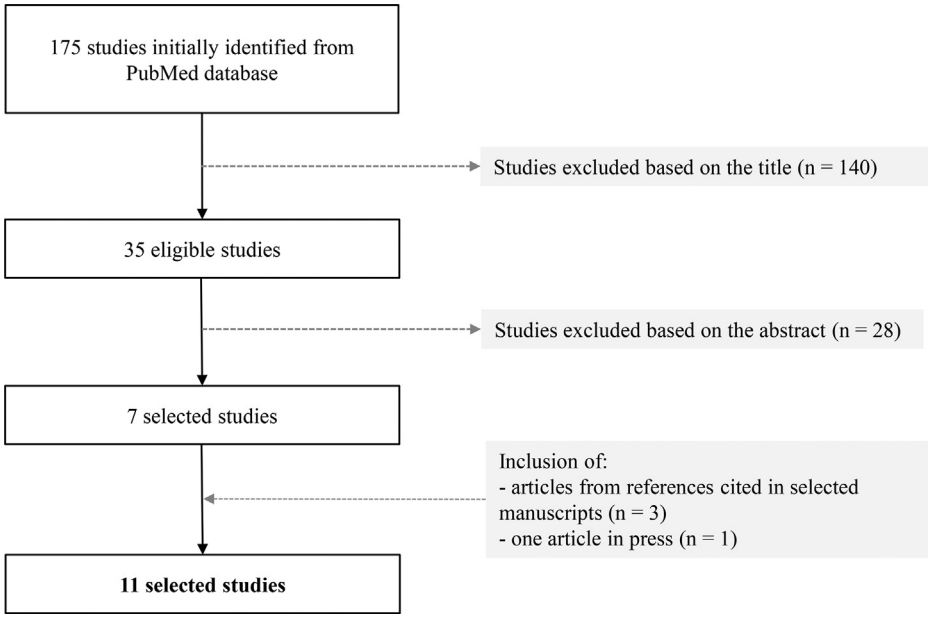

Figure 1 Flow-chart.

Nevertheless, postural instability is also present in the early stages before any visible balance disturbances [3,5,19]. The result of this review suggests that measures of gait and balance could be used as early markers of preclinical PD.

Both clinical (i.e., Timed Up and Go Test, Stand-Walk-Sit Test, 6-Meter Corridor Walk Test) and instrumental (Vicon®, GAITRite®, 3-axis accelerometer) assessments allow for early detection of gait and balance disorders. Only one study performed concomitant clinical and instrumental gait assessments, with similar results whatever the method used, notably gait slowing [6]. PD affects 1% of people over the age of 65 years and approximately 4% of the population aged over 80 years. In order to detect individuals at-risk of developing PD, we need to identify markers, which can be used in people aged over 50 years. The method used needs to be easily accessible, simple to use, without specific equipment and with little training, inexpensive and quick. Clinical methods clearly seem to meet all requirements, although further studies are needed to compare the sensitivity and specificity of clinical versus instrumental assessments.

Gait and balance disorders become more apparent under challenging walking (i.e., fast-paced, dual-task) and standing (i.e., vision deprivation, on foam support, in tandem position) conditions, respectively. Challenging the central gait network with demanding tasks is a relevant approach to uncover abnormalities and thus unmask compensatory mechanisms among asymptomatic subjects. Gait variability, as quantified by the number of step-to-step fluctuations in time (i.e. temporal gait variability) or space (i.e. spatial gait variability), has recently developed into a measure of interest due to its potential utility as a predictive marker of PD and other neurodegenerative conditions [8,13,37]. Among the studies reviewed, temporal gait variability was measured in three studies [21,22,24] and spatial gait variability in one study [21]. Gait disorders related to preclinical PD manifest through increased temporal gait variability (i.e., stride time variability, double support time variability, and swing time variability). Moreover, impairment in temporal automaticity of gait occurs under challenging conditions (fast pace walking and dual-task walking) without other gait abnormalities, notably preserved gait speed, stride length and stride time [22,24], suggesting that greater variability in temporal parameters may be particularly sensitive to preclinical PD. Arm kinematics was measured in three studies [24,26,36] and seems to provide a sensitive measure of decline in gait function in preclinical PD. Indeed, arm swing variability increases during dual-task walking with no apparent changes in the other studied parameters (i.e., gait speed, stride length and stride time) [24]. Taken together, these findings suggest that temporal gait variability and arm kinematics, particularly under challenging conditions, may represent potential specific markers of preclinical PD.

Preclinical markers are of interest for early identification of people who are likely to develop PD in the future. Nevertheless, whereas idiopathic PD represents 90% of PD, this review underlines the fact that only one study was conducted in individuals who developed idiopathic PD. Other studies concerned individuals with either genetic PD or at higher risk for PD, but preclinical markers derived from these studies cannot necessarily be generalized to the population of patients with idiopathic PD. Genetic PD represents 10% of PD. Many forms of familial PD of Mendelian inheritance have been brought to light, either with recessive inheritance or with dominant inheritance. To date, two forms of genetic PD have been investigated to identify preclinical markers: *LRRK2* gene mutation and *PINK1* gene mutation. Mutations in the *LRRK2* gene are responsible for 1%—2% of sporadic and 4% of familial PD with autosomal dominant inheritance. Non-manifesting carriers of LRRK2 mutations represent those at higher risk for PD. Hence, the exploration of genetic PD allows evaluation of disease manifestations at the prodromal stage. The phenotype of PD with LRKK2 mutation largely overlaps that of idiopathic PD [20]. Nevertheless, gait disorders in patients with LRKK2 mutation

Table 1 Summary of the articles selected for the review.

	First author *Journal*, year	Population characteristics	Posturo-locomotor assessments			Main findings
			Assessment type	Tasks	Parameters	
Genetic PD	Mirelman *Annals of Neurology*, 2011 [22]	Non-manifesting LRRK2 mutation carriers ($n = 25$, age = 53.6 years) Controls ($n = 27$, age = 50.1 years)	Instrumental gait assessment with an accelerometer worn on the lower back	Walking along a 20-meter long corridor (1 minute) Single-task walking at usual and fast pace, dual-task walking at usual pace	Gait speed, stride length, stride time, stride time variability	Stride time variability higher among the mutation carriers under single-task walking at fast pace and dual-task walking Gait speed, stride time and stride length similar in both groups under all walking conditions
	Mirelman *Movement Disorders*, 2016 [24]	Non-manifesting LRRK2 mutation carriers ($n = 122$) Non-manifesting LRRK2 mutation non-carriers ($n = 64$)	Instrumental gait assessment with accelerometers on the lower back and on both wrists	Walking along a 15-meter long corridor (1 minute) Single-task and dual-task walking at usual pace	Gait speed, stride time, stride time variability, arm swing (amplitude, asymmetry, variability, jerk), axial body rotation amplitude, axial body rotation jerk	During dual-task walking only, non-manifesting carriers had: higher stride time variability; higher arm swing asymmetry, arm swing variability, and jerk; higher axial rotation jerk; when compared with non-manifesting non-carriers
	Van Den Heuvel *Journal of Parkinson's Disease*, 2018 [36]	Non-manifesting LRRK2 mutation carriers ($n = 14$, age = 62 years) Controls ($n = 26$, age = 55 years)	Instrumental gait assessment with actigraphs on both wrists	Walking in a straight line at usual pace (2 minutes) and fast pace (1 minute)	Arm movement variability	Non-manifesting carriers showed higher arm swing variability during single-task walking
	Nürnberger *Movement Disorders*, 2015 [26]	Heterozygote PINK1 mutation carriers without definite PD ($n = 9$, age = 47.1 years) Controls ($n = 25$, age = 44.8 years)	Instrumental gait assessment with an ultrasound-based 3D motion analysis system	Walking on a treadmill at 3.5 $km.h^{-1}$ (30 seconds)	Arm swing amplitude, arm anteversion and retroversion	PINK1 mutation carriers showed bilateral reduction of arm swing amplitude and arm anteversion

Table 1 (*Continued*)

	First author *Journal*, year	Population characteristics	Posturo-locomotor assessments			Main findings
			Assessment type	Tasks	Parameters	
Increased risk of PD	Chen *Brain Research*, 2014 [7]	REM sleep behavior disorder ($n = 24$, age = 65.4 years) Controls ($n = 23$, age = 64.2 years)	Instrumental balance assessment with an accelerometer worn on the 4—5th lumbar spine segment	Standing upright: single-task feet together EO and EC, dual-task feet together EO and EC, single-task tandem position EO	Postural sway: root mean square acceleration and sway jerkiness	Increased variability of trunk acceleration and increased sway jerkiness in RBD only under challenging conditions (dual-task feet together EO and EC, single-task tandem standing EO)
	Ellmore *Parkinsonism & Related Disorders*, 2010 [9]	REM sleep behavior disorder ($n = 5$, age = 52.6 years) Controls ($n = 7$, age = 54.0 years) Early PD ($n = 5$, age = 60.0 years)	Clinical gait assessment by a timed gait task	Stand-walk-sit	Gait and transfer speed	No significant differences between the two groups
	McDade *Movement Disorders*, 2013 [21]	Probable REM sleep behavior disorder ($n = 42$, age = 79.0 years) Controls ($n = 492$, age = 79.4 years)	Instrumental gait assessment with GAITRite® system	Walking for 10 meters at usual pace	Gait speed, stride length, cadence, swing and stance time, double support time; and variability of stride length, stride time, swing and stance time, double support time	Probable RBD had: decreased gait speed and cadence; increased double support time variability, stride time variability and swing time variability
	Postuma *Neurology*, 2006 [27]	REM sleep behavior disorder ($n = 25$, age = 69.2 years) Controls ($n = 25$, age = 69.2 years)	Clinical gait assessment by a Timed Up and Go test	Rise quickly from a chair, walk 3 meters, turn, and return to sit in the same chair	Gait and transfer speed	RBD took longer to perform the Timed Up and Go Test
	Postuma *Brain*, 2012 [30]	RBD patients who developed parkinsonism ($n = 20$, age = 70.5 years) Controls ($n = 40$, age = 70.1 years)	Clinical gait assessment by a Timed Up and Go test	Rise quickly from a chair, walk 3 meters, turn, and return to sit in the same chair	Gait and transfer speed	Performance of the Timed Up and Go Test became abnormal 4.4 years before parkinsonism diagnosis

Table 1 (*Continued*)

	First author *Journal*, year	Population characteristics	Posturo-locomotor assessments			Main findings
			Assessment type	Tasks	Parameters	
	Maetzler *PLOS One*, 2012 [18]	Patients at high-risk of PD ($n = 20$, age = 61.9 years) PD ($n = 12$, age = 61.5 years) Controls ($n = 14$, age = 63.9 years)	Instrumental balance assessment with an accelerometer worn on the 3—4th lumbar spine segment	Standing upright in semi-tandem position: on the ground EO and EC, on a foam support EO and EC	Postural sway: root mean square acceleration, mean sway velocity, and sway jerkiness	Increased variability of trunk acceleration and increased sway jerkiness in patients at high-risk of PD in the most challenging condition (EC on a foam support)
Sporadic PD	Chastan *Gait & Posture*, 2018 [6]	Prediagnosed idiopathic Parkinson's disease ($n = 10$, age = 79.4 years) Controls ($n = 30$, age = 79.5 years)	Clinical gait and balance assessment, and instrumental gait assessment with a Vicon® system	A 6-meter corridor walk at usual and fast pace, and a 400-meter corridor walk at fast pace Walking for 10 meters at usual and fast pace (Vicon®) Standing upright: semi-tandem position, tandem position, and one-leg Interview on balance when walking	Gait speed, cadence, step and stride length, step and stride time, stance and swing time, single support time, step width Time to perform standing tasks	Prediagnosed idiopathic PD: had slower gait speed (6-meter walk test and Vicon®), shorter step and stride length (Vicon®); reported more impaired balance when walking compared to controls; no differences for the timed standing tasks

EC: eyes closed; EO: eyes open; LRRK2: Leucine-rich repeat kinase 2; PD: Parkinson's disease; PINK1: PTEN-induced putative kinase 1; RBD: REM sleep behavior disorder; REM: rapid eye movement.

are different to those in patients with idiopathic PD [23,24], independently of the type of assessment (clinical or instrumental). LRRK2 mutation carriers take longer to perform the Timed Up and Go Test and show more frequent falls and lower gait regularity (i.e., greater stride time variability and arm swing variability). It is possible that the gait network of LRRK2 mutation carriers is simply different, unrelated to the future development of PD (i.e., an endophenotypic marker and not a specific marker of PD) [22]. Moreover, LRRK2 mutations have incomplete and age-dependent penetrance [14]. Incomplete penetrance means that a proportion of the non-manifesting LRRK2 mutation carriers will never develop prodromal symptoms. Age-dependent penetrance means that the risk of PD for a LRRK2 mutation carrier increases with age [14].

Mutations in the *PINK1* gene are responsible for familial PD with autosomal recessive inheritance. The phenotype of PD with PINK1 homozygous mutations resembles that of sporadic PD but differs in several aspects. Indeed, PINK1 homozygous mutation carriers show symptoms earlier, slower disease progression, better response to levodopa, but with levodopa-induced dyskinesia in the long-term [1]. Therefore, this population provides an opportunity to study the natural course of at least some motor symptoms from the earliest stages of the disease. Individuals with a single heterozygous PINK1 mutation are either clinically asymptomatic or reveal subtle parkinsonian motor signs, albeit not fulfilling the diagnostic criteria of definite PD [15]. Therefore, it is likely that preclinical markers found in this population cannot necessarily be generalized to a population with sporadic PD.

Patients at high-risk of developing PD manifest REM sleep behavior disorder (RBD). RBD is a rare form of REM sleep-related parasomnia with an estimated prevalence rate of 0.5% in the general population [32]. Clinically, polysomnography monitoring is mandatory for accurate diagnosis of

RBD, which is characterized by abnormal muscle activity during REM sleep. Abnormalities consist of either sustained muscle activity in REM sleep in chin electromyography (EMG) or as excessive transient muscle activity in REM sleep in chin or limb EMG. RBD patients have excessive motor activity, such as punching, kicking or crying out, in response to dream content during REM sleep, instead of normal muscle atonia. RBD is commonly associated with neurodegenerative disorders characterized by abnormal accumulation of α-synuclein. Longitudinal studies estimate that over 50% of patients with idiopathic RBD will develop neurodegenerative parkinsonian syndromes, almost exclusively PD, but also multiple system atrophy, progressive supranuclear palsy or dementia with Lewy bodies [17,29,33]. As many patients with RBD are at-risk of developing PD, it is crucial to identify potential markers of preclinical PD, which may be present in patients with RBD. However, patients with RBD and PD have different clinical manifestations (phenotypes) than PD patients without RBD, suggesting that they may present different underlying patterns of neurodegeneration. Specifically, patients with RBD and PD are more prone to falling (38% versus 7%) and less responsive to their medication dose [28]. RBD reflects dysfunction of brainstem regions that regulate both REM sleep and gait control. Thus, these findings should be interpreted cautiously as we cannot exclude the fact that the deficits of idiopathic RBD patients might reflect, at least in part, endophenotypic markers, and not specific markers of preclinical PD. Moreover, some patients with idiopathic RBD may develop parkinsonian syndrome (and not PD), for whom balance and gait disorders occur earlier, and sometimes represent predominant symptoms, as in progressive supranuclear palsy.

Conclusion

Measures of gait and balance could be early markers of preclinical PD. Further studies are needed to identify more specific and more sensitive markers to detect individuals at-risk of developing idiopathic PD. To this end, large longitudinal studies should be conducted, in populations experiencing natural aging, in which idiopathic PD cases occur [35], instead of cross-sectional studies among individuals with either genetic PD or at high-risk of developing PD. Assessing subtle gait and balance abnormalities may be an inexpensive and efficient method to initially screen for at-risk individuals, that could subsequently be completed by more thorough screening as transcranial sonography of the substantia nigra.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

The authors are grateful to Nikki Sabourin-Gibbs for her help in editing the manuscript.

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