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Head and trunk stability during gait before and after levodopa intake in Parkinson's disease subtypes

Paulo H.S. Pelicioni[a,b], Matthew A. Brodie[a], Mark D. Latt[c], Jasmine C. Menant[a,b], Hylton B. Menz[d], Victor S.C. Fung[e], Stephen R. Lord[a,b,*]

[a] Neuroscience Research Australia, Barker street, Randwick 2031, Sydney, New South Wales, Australia
[b] School of Public Health and Community and Medicine, University of New South Wales, Samuels Avenue, Kensington, 2033 Sydney, New South Wales, Australia
[c] Department of Aged Care, Royal Prince Alfred Hospital, 50 Missenden road, Camperdown, 2050 Sydney, New South Wales, Australia
[d] School of Allied Health, College of Science, Health and Engineering, La Trobe University, 1300 La Trobe, Melbourne, Victoria, Australia
[e] Department of Neurology, Westmead Hospital, Hawkesbury road and Darcy road, Westmead, 2145, Sydney, New South Wales, Australia

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ABSTRACT

Introduction: People with Parkinson's disease (PD) can be classified into tremor dominant (TD) and postural instability and gait difficulty (PIGD) subtypes; the latter group having more impaired gait and increased fall risk. While there is some evidence that anti-parkinsonian medication, levodopa, might not improve balance and gait control or reduce fall risk in the PIGD subtype, it is unclear whether the levodopa dosage intake affects gait stability. To address these issues, this study used accelerometry to compare gait stability: (i) during before and after levodopa intake between non-PIGD and PIGD subtypes; (ii) between individuals who took less or > 750 mg of levodopa/day.

Methods: In 15 non-PIGD (Combination of 13 TD patients and 2 classified as indeterminate subtype) and 23 PIGD participants of similar mean (SD) age ((63.0 (7.6) versus 62.6 (10.0) years, respectively)) and disease-duration (8.9 (8.9) versus 11.3 (4.6) years, respectively), head and trunk stability during gait was examined using anteroposterior, vertical and mediolateral acceleration harmonic ratios (HRs). Participants were assessed before and after a levodopa dose, during typical "off" and "on" periods, respectively.

Results: Two-way analyses of variance (group × medication status) revealed that compared to the non-PIGD subgroup, the PIGD subgroup showed significantly worse head stability (lower anteroposterior HR) in the "off" state, and significantly worse pelvis stability (significantly lower mediolateral and vertical HRs) in the "on" state ($p < 0.05$ for both). Levodopa was effective in treating most of the disease-related impairments (not bradykinesia) in both groups, ($p < 0.05$) but improved gait stability (lowered pelvis mediolateral and vertical HRs) only in people with the non-PIGD subtype ($p < 0.05$) and those taking < 750 mg of levodopa/day ($p < 0.05$).

Conclusions: People with the PD PIGD subtype exhibit impaired gait stability that is not improved and frequently worsened by levodopa. New non-pharmaceutical approaches, technological (e.g. cueing) or exercise-based (e.g. balance training) are required to improve or compensate for mediolateral gait instability in this subtype and ultimately prevent falls.

1. Introduction

Parkinson's disease (PD) is a heterogeneous neurological disease with a range of motor and non-motor signs and symptoms (Jankovic et al., 1990). These include postural instability and gait disturbances which are particularly debilitating as they predispose people with PD to fall (Paul et al., 2016). In addition to well documented slower gait speed, shorter step length and higher step timing variability (Galna et al., 2015; Latt et al., 2009; Hausdorff, 2005), studies using wearable sensors have shown that people with PD have irregular trunk and head movements in anteroposterior (AP) and mediolateral (ML) planes when walking (Latt et al., 2009; Brodie et al., 2014), and that such uncontrolled gait patterns are more apparent in those who suffer falls (Latt et al., 2009).

The degenerative nature of PD is unclear due to genetic and environmental factors and manifests itself in a broad range of motor clinical characteristics such as bradykinesia, resting tremor, rigidity, postural instability and gait disorders. Yet the presentation of these

* Corresponding author at: Neuroscience Research Australia, Barker Street, Randwick, New South Wales 2031, Australia.
E-mail address: s.lord@neura.edu.au (S.R. Lord).

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syndromes is heterogeneous across people with PD, making it difficult to intervene on. With the intention of tailoring treatments, some researchers have categorized people with PD with respect to time since onset (Abdullah et al., 2015) or disease subtype (Jankovic et al., 1990). For example, people with PD have been categorized into two subtypes based on their motor features: Tremor Dominant (TD), with a predominance of resting and postural tremor, and Postural Instability and Gait Difficulty (PIGD) with a predominance of postural instability and gait impairment (Jankovic et al., 1990). This classification is usually based on an ascertainment of fall history and clinical balance and gait assessments from the Unified Parkinson's Disease Rating Scale (UPDRS) examination of the parts II and III, and while it has been suggested this motor subtype classification may reflect different stages of Parkinson's disease rather than different disorders (Nutt, 2016), it may be important for identifying people with PD at increased fall risk and elucidating underlying causes of falls.

However, only a few studies have contrasted gait control between the subtypes. This work has shown people with the PIGD subtype have step-by-step asymmetry (Pasciuto et al., 2017) (represented by lower harmonic ratio (HR) values assessed with accelerometry) in a three-day home assessment (Herman et al., 2014) and that those with the PIGD subtype have more pace and variability gait impairments in both the "off" and "on" antiparkinsonian medication states (Galna et al., 2015; Lord et al., 2014; Vervoort et al., 2015). These studies have used electronic walkways to record overall stability indices or restricted their accelerometry assessments to the pelvis only. As such, they have not been able to document head stability, a key marker of gait control and fall avoidance (Latt et al., 2009; Menz et al., 2003).

Further, little research has contrasted the effects of antiparkinsonian medication on gait stability between the PD subgroups. While levodopa and dopamine agonist therapy attenuates some motor signs and symptoms (Tomlinson et al., 2010), it does not appear to improve balance and gait control or reduce fall risk (Curtze et al., 2015). This may be particularly the case for people with the PIGD subtype as they have both a lower absorption and response to dopamine (Mo et al., 2010). To our knowledge, whether levodopa dosage differentially affects gait stability measures between PD subtypes is still unknown. To address the above issues, we compared head and trunk stability during gait with wearable sensors in non-PIGD and PIGD groups and their response to levodopa treatment. We hypothesized that: (i) the PIGD group would have significantly worse gait stability compared with the non-PIGD group, (ii) levodopa treatment would improve gait stability to a lesser extent in the PIGD than in the non-PIGD group and (iii) participants with high daily levodopa doses would show differential gait stability responses to levodopa depending on their subtype.

2. Methods

2.1. Participants

Thirty eight participants from community-based PD support groups volunteered to participate in the study. Participants were eligible if they had a diagnosis of idiopathic PD according to the UK PD Brain Bank criteria (Hughes et al., 1992), lived in the community, were able to walk unassisted and without ambulation aids during a gait assessment, did not have any other neurological or cognitive impairment and were aged 40 years or older. The protocol was approved by the Human Studies Ethics Committee at the University of Sydney and informed consent was obtained from all participants prior to their participation.

2.2. UPDRS assessments and participant classification

Participants attended the gait laboratory at Neuroscience Research Australia on two occasions ("on" and "off" medication) on the same day to complete a series of walking trials. UPDRS assessments obtained the following scores: Rigidity (sum of upper and lower limb scores); Axial Posture; Bradykinesia; Dyskinesia; Motor complications; Motor Impairments (UPDRS part III); and total UPDRS (Table 1) (Fahn and Elton, 1987). Also, the stage of the disease was analyzed using the Hoehn and Yahr stage (Hoehn and Yahr, 1967).

Table 1
Demographic, anthropometric and disease-related measures in the "off" state for the Non-PIGD and PIGD groups. Data are mean ± SD unless stated otherwise.

	Non-PIGD	PIGD	p
	(n = 15)	(n = 23)	
Demographic/Antropometric			
Sex Male (%)	8 (53)	15 (65)	0.514
Age (years)	63.0 ± 7.6	62.6 ± 10.0	0.892
Height (cm)	173.5 ± 7.1	170.9 ± 10.1	0.359
Weight (kg)	74 ± 9.1	71 ± 11.5	0.384
Disease-related			
Previous fallers (%)	13 (57)	4 (27)	0.140
Duration of disease (years)	8.9 ± 8.9	11.3 ± 4.6	0.283
Levodopa dosage intake (%)			
< 750 mg (total n = 22)	12 (80)	10 (43)	**0.002**
> 750 mg (total n = 16)	3 (20)	13 (57)	
UPDRS total score	33.5 ± 20.7	45.8 ± 15.5	**0.041**
UPDRS part III score	16.3 ± 11.4	22.4 ± 10.9	0.097
Hoehn and Yahr score	2.2 ± 0.9	1.5 ± 0.7	0.067
Rigidity score	2.7 ± 2.9	3.1 ± 2.1	0.391
Axial Posture score	0.4 ± 0.6	1.3 ± 0.8	**0.001**
Bradykinesia score	0.6 ± 0.7	1.4 ± 1.1	**0.017**
TD score	4.5 ± 3.1	1.3 ± 1.1	< **0.001**
PIGD score	1.6 ± 1.4	5.3 ± 2.7	< **0.001**
Dyskinesia (%)	5 (33.3)	8 (34.8)	0.927
Motor complications	4.5 ± 3.4	4.0 ± 2.4	0.813

UPDRS: Unified Parkinson's Disease Rating Scale; TD: Tremor Dominant; PIGD: Postural Instability and Gait Difficulty. Significant differences in bold.

The mean tremor score was calculated as the mean of UPDRS part II, item 16 (tremor) and UPDRS part III, items 20 (rest tremor) and 21 (action tremor) scores. The mean PIGD score was calculated as the mean of UPDRS part II, items 13 (falling), 14 (freezing) and 15 (walking) and UPDRS III, items 29 (gait) and 30 (postural stability) (Jankovic et al., 1990). The ratio of mean tremor score to mean PIGD score was used to determine motor subtype: ratios ≥ 1.5 identified subjects with the TD subtype (n = 13), ratio scores ≤ 1.0 the PIGD subtype (n = 23) and ratios between 1.01 and 1.49 the indeterminate subtype (n = 2). Due to relatively small sample numbers, the TD and indeterminate groups were combined to form a single non-PIGD group (n = 15) for subsequent analyses (Jankovic et al., 1990).

2.3. Gait assessment

The gait analysis was performed using linear accelerometers (Menz et al., 2003). One tri-axial piezo-resistant accelerometer was attached to the participant's head using a light plastic helmet liner (combined weight 62 g) and a second was attached mid back at the level of the sacrum. The head accelerometer's local z-axis was aligned with the global vertical, the AP axis projected onto a line connecting the base of skull and sellion pointing forwards, and the ML axis was aligned right to left according to the right hand rule. The pelvis accelerometer was rigidly attached between the posterior iliac spines using adhesive and a thick Velcro belt to reduce soft tissue artefacts. For each walking trial, data were reported according to a global vertical, body-centred heading, reference system (Brodie et al., 2015a). As such, small pitch and roll corrections were applied to the sensor data so that the movements of the head and pelvis in the VT direction were aligned with the global vertical. The AP axes pointed forwards and parallel to the floor and the ML axes were aligned right (−ve) to left (+ve) across the direction of travel. Participants performed 2 walking trials in total (one in "off" state of medication and one in "on") at a self-selected speed along