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Contributions of mild parkinsonian signs to gait performance in the elderly

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Abstract Mild parkinsonian signs (MPS) and gait abnormalities are common in aging, but the association between MPS and objective gait measures is not established in the elderly. This study aims to identify the link between MPS and quantitative gait measures, as well as to determine the pathogenesis of MPS in non-demented community-dwelling older adults without idiopathic Parkinson's disease or other parkinsonian syndromes. Three hundred seventy-four non-demented older adults (mean age, 76.44±6.71 years, 57 % women) participated in this study, where comprehensive neurological and medical assessments were conducted. We defined MPS based on the presence of any one of bradykinesia, rigidity, or rest tremor. Velocity and spatial, temporal, and variability gait parameters were recorded using an instrumented walkway. The associations of MPS and gait parameters as well as the relationship of individual MPS with medical illnesses were assessed with linear regressions controlling for key covariates. Participants with MPS walked slower and with disturbed spatial and variability components of gait compared to those without MPS. Bradykinesia was associated with worse spatial and variability gait parameters. This association was only significant for axial bradykinesia, but not for the presence of bradykinesia in the limbs. Cerebrovascular disease ($\beta = .20$, $p < .01$) was associated with bradykinesia, whereas cardiovascular disease ($\beta = .15$, $p < .05$) was associated with rigidity. Among MPS, bradykinesia but not rigidity or tremor was associated with worse quantitative gait performance in older adults. Cerebrovascular disease, a preventable condition, was specifically associated with bradykinesia.

Keywords Gait · Aging · Mild parkinsonian signs · Cerebrovascular disease

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Introduction

Mild parkinsonian signs (MPS) occur in 15 to 52 % of elders, even in the absence of parkinsonian syndromes (Bennett et al. 1996). Though MPS have been considered by some to be benign signs of aging, investigators have reported their association with functional disability (Fleischman et al. 2007; Louis et al. 2005b), depression (Uemura et al. 2013), and dementia (Louis et al. 2004, 2010). Murray et al. (2004) found that functional decline was specifically associated with the presence of gait disorders and bradykinesia, but not with other MPS such as rigidity or tremor. Similarly, neuroimaging studies reveal that white matter lesions in the frontal and parietal

lobes were linked to bradykinesia (de Laat et al. 2012) and gait disturbances (de Laat et al. 2010), suggesting a shared pathway between bradykinesia and gait in aging.

Quantitative gait has also been linked to risk of disability, falls, and dementia in healthy older adults (Verghese et al. 2009). Basal ganglia and their connections with frontal lobes are involved in the pathophysiological mechanisms of MPS in the elderly (Louis and Bennett 2007) and contribute to the control of gait, especially in the regulation and timing of gait (Maillet et al. 2012; Grabli et al. 2012). Regarding parkinsonian signs, patients with Parkinson's disease (PD) manifest slower gait velocity due to a reduction of step length with an unchanged cadence (Stolze et al. 2001). While some of these gait disturbances are dopa-sensitive, others are dopa-resistant (Blin et al. 1991), suggesting alternative or additional mechanisms than just dopamine deficiency. However, the relationship between quantitative gait parameters and individual MPS in aging is not known at present. In most studies, the definition of MPS includes postural instability and gait disturbances (PIGD), making it difficult to interpret the association of MPS with gait parameters in older adults with normal gait and presumably in earlier pathological stages.

To address the knowledge gap regarding the association of individual MPS and quantitative gait performance in aging, we conducted a study in a cohort of community-residing non-demented older adults without idiopathic PD or other parkinsonian syndromes. Since it is likely that PIGD items would be strongly correlated with objective quantitative gait parameters, here, we included bradykinesia, rigidity, and rest tremor and excluded items that measure postural instability and gait in our operational definition of MPS. Given the reported link between bradykinesia and gait (Murray et al. 2004) and the role of basal ganglia in the control of gait (Maillet et al. 2012; Grabli et al. 2012), we hypothesized that bradykinesia would be most strongly associated with quantitative gait performance, especially with spatial and variability parameters. Further, to better understand the pathogenesis of MPS in aging, our secondary aim was to determine the relationship of individual MPS—bradykinesia, rigidity, and tremor—with medical illnesses, including cardiovascular and cerebrovascular diseases.

Methods

Participants

Four hundred twenty-five non-demented adults age 65 and older were recruited from an ongoing cohort study entitled Central Control of Mobility in Aging (CCMA; Holtzer et al. 2014). The primary aim of the CCMA study is to determine cognitive and brain predictors of mobility in aging. Consensus diagnostic case conferences were conducted to assure that participants did not meet the criteria for dementia (Holtzer et al. 2008). Participants were excluded from this study if they did not complete a neurological examination (n=37), had idiopathic PD (n=7), were missing quantitative gait assessments (n=6), or were prescribed dopamine-blocking agents/neuroleptics (n=1). Following exclusions, 374 non-demented ambulatory older adults were included in this analysis. The Institutional Review Board approved the experimental procedures, and all participants provided written informed consent in accordance with the tenets of the Declaration of Helsinki.

Clinical assessment and mild parkinsonian signs

Comprehensive neurological examination included assessment for clinical gait abnormalities, medical illnesses, and MPS. Neurological gait abnormalities were diagnosed by the study clinician as previously described (Verghese et al. 2002). Global health status (GHS; range 0–10) was obtained from dichotomous rating (presence or absence) of medical illnesses, including diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, PD, chronic obstructive pulmonary disease, angina, and myocardial infarction (Verghese et al. 2007b).

MPS were systematically ascertained in participants by the clinician using the motor evaluation portion (part III) of the original Unified Parkinson's Disease Rating Scale (UPDRS), a test with moderate reliability and validity (Fahn and Elton 1987). Severity indices for individual MPS (i.e., bradykinesia, rigidity, and tremor) were calculated by summing clinician ratings (0–4) across 3 domains: (1) bradykinesia in extremities (peripheral) was assessed with finger tapping, hand movements, rapid alternating hand movements, and leg agility (UPDRS#23–26) and body (general or axial) bradykinesia was assessed by combining, slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general (UPDRS#31); (2)

rigidity in extremities (peripheral) and neck (axial) was judged on passive movement of major joints with patients relaxed in sitting position while cogwheeling was ignored (UPDRS#22); and (3) occurrence of tremor at rest was only assessed in extremities (UPDRS#20). Note, as previously stated, UPDRS questions assessing posture and gait were purposefully excluded from our definition of MPS, as inclusion of these domains would likely render circular analyses. Since no gold standard assessment of MPS exists in normal aging, we employed a "sensitive approach" to operationalize the presence of MPS. Here, individuals with scores greater than zero on the UPDRS rating on any one domain (i.e., bradykinesia, rigidity, or tremor) were considered to have MPS in an attempt to identify markers of abnormal motor aging occurring in very early stages. We acknowledge that this sensitive method limits the specificity of the examination and, therefore, recommend that this approach serves as a screening tool rather than a precise marker of MPS severity.

Depression was measured using the Geriatric Depression Scale (GDS) where a cutoff score >9 was used to define the presence of any depression symptomology from mild to severe (Yesavage et al. 1982). The clinician also documented osteoarthritis and vascular conditions, as these medical illnesses, as well as depression, have been previously associated with MPS (Louis and Bennett 2007). Vascular conditions were categorized as cerebrovascular disease (stroke or transient ischemic attacks), cardiovascular disease (myocardial infarction, angina, arrhythmia, and chronic heart failure), and cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia, body mass index >30, and smoking). Additionally, physical activity level was measured by asking participants how many days per month (0–30) did they participate in exercise or sports? (Verghese et al. 2003).

Quantitative gait assessments were conducted using a 28-ft instrumented walkway with embedded pressure sensors (GAITRite, CIR Systems, Havertown, PA). The GAITRite system is widely used in clinical and research settings and has excellent psychometric properties (Verghese et al. 2007a). The walkway has 4 ft at each end without sensors to account for initial acceleration and terminal deceleration. Briefly, participants were asked to walk on the mat at their 'normal walking speed' in a quiet and well-lit room, as previously described (Verghese et al. 2002). In addition to gait velocity, we chose two spatial parameters (stride width and stride length), two temporal parameters (stride time and swing time), and two measures of variability (stride length and swing time variability), where the coefficient of variability (COV) was calculated following this formula: COV=standard deviation/mean). The selection of gait parameters was based on the highest loading gait variables in different gait domains identified by factor analysis that we performed in another cohort (Verghese et al. 2007b).

Several studies have demonstrated an association between MPS and cognitive deficits in aging (Richards et al. 1993; Louis et al. 2004, 2005a, 2010; Boyle et al. 2005). As the focus of this study was to examine the association between MPS and gait performance, we did not attempt to corroborate previous findings, but rather sought to determine the contribution of cognition to individual MPS. Global cognition was assessed using the total scale score of the Repeatable Battery for Assessment of Neuropsychological Status (RBANS). The RBANS is a brief cognitive test with several alternate forms that measures immediate and delayed memory, attention, language, and visuo-spatial skills. The RBANS also provides a total index score, which provides an overall assessment of global cognitive function and is useful for the detection and characterization of dementia in older adults (Duff et al. 2008).

Statistics

Pearson correlations were conducted to determine associations between individual MPS and quantitative gait parameters. Significant associations were further examined in multivariate linear regression analyses adjusted for age, gender, education level, clinical gait abnormalities, medical illnesses, and physical activity in an effort to determine the association of individual MPS (independent variables) with quantitative gait parameters (dependent variables). All data analyses were run using SPSS Version 20, and corrections for multiple comparisons were applied if needed.

To determine whether bradykinesia and rigidity were associated with medical conditions (cardiovascular disease, cerebrovascular disease, cardiovascular risk factors, osteoarthritis, depression, and cognition) previously linked with MPS (Louis and Bennett 2007), multivariate linear regressions with adjustments for age, gender, and education level were performed.

To examine associations of the location of bradykinesia (either peripheral or axial; independent variables)

with quantitative gait parameters (dependent variables), follow-up multivariate regressions were conducted. These analyses were adjusted for age, gender, clinical gait abnormalities, and multiple comparisons.

Results

Characteristics of the sample are provided in Table 1. All participants were deemed relatively healthy and cognitively intact as determined by their GHS and RBANS scores. Forty-six percent of the sample presented with MPS. Rigidity was the most common MPS (37 %), followed by bradykinesia (21 %) and rest tremor (3 %). Quantitative gait data for the entire cohort, as well as for individuals subdivided into those without MPS (n=203) and those with MPS (n=171) are presented in Table 1. Overall, participants with MPS had worse performance on multiple gait parameters compared to participants without MPS. Participants with bradykinesia, rigidity, and tremor demonstrated 30, 37, and 75 % prevalence of clinical gait abnormalities, respectively. Table 2 delineates the total UPDRS values for bradykinesia, rigidity, and tremor as well as scores by location. Results indicated no significant association of tremor with any gait parameter and no significant association of stride time with any individual MPS.

Severity of bradykinesia was associated with worse performance on velocity, spatial gait parameters (stride length and stride width), and measures of variability of stride length and swing time even after adjustments for confounders and multiple comparisons (Table 3).

Table 1 Sample Characteristics

		Overall (n=374)	No MPS (n=203)	MPS (n=171)
Demographics	Age (years)	76.44 (6.71)	74.85 (6.22)	78.33 (6.80)
	Education (years)	14.38 (3.07)	14.39 (3.15)	14.36 (2.99)
	% Female	57.00	57.00	57.00
MPS domains	Bradykinesia (% present)	21.00	0.00	46.00
	Rigidity (% present)	37.00	0.00	80.00
	Tremor (% present)	3.00	0.00	7.00
Clinical	% with cardiovascular disease	24.00	22.00	28.00
Covariates	% with cerebrovascular disease	7.00	5.00	10.00
	% with cardiovascular risk factors	74.00	68.00	81.00
	% with osteoarthritis	46.00	40.00	53.00
	GHS Score (0–10)	1.74 (1.21)	1.52 (1.20)	2.00 (1.19)
	GDS Score (0–30)	4.61 (3.97)	4.00 (3.47)	5.42 (4.42)
	RBANS Total Standard Score (55–145)	91.83 (12.12)	93.43 (11.89)	89.88 (12.15)
	Physical activity level (exercise days/month; 0–30)	12.81 (10.57)	12.83 (10.53)	12.79 (10.67)
Gait	% with normal gait	52.00	65.00	37.00
	Velocity (cm/s)	99.09 (22.70)	104.27 (20.82)	92.95 (23.36)
	Stride length (cm)	115.85 (20.31)	121.20 (17.96)	109.50 (21.14)
	COV stride length (%)	2.90 (1.91)	2.57 (1.59)	3.28 (2.18)
	Stride time (s)	1.19 (.15)	1.18 (0.14)	1.20 (0.16)
	Swing time (s)	0.40 (.05)	0.41 (0.04)	0.40 (0.05)
	COV swing time (%)	4.63 (2.81)	4.26 (2.44)	5.07 (3.15)
	Support base (cm)	9.94 (4.17)	9.29 (4.21)	10.70 (4.01)
	Double support time (s)	0.38 (.10)	0.36 (0.08)	0.40 (0.11)
	Cadence (steps/min)	102.51 (12.16)	103.24 (11.69)	101.64 (12.68)

Mean (SD) unless otherwise noted

MPS mild parkinsonian signs, *GHS* Global Health Score, *GDS* Geriatric Depression Scale, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *COV* coefficient of variability

Table 2 UPDRS scores [mean±(SD)] by domain and location for individuals with MPS (n=171)

	Bradykinesia	Rigidity	Tremor
Peripheral	1.46 (2.64)	2.36 (2.20)	0.15 (0.67)
Axial	0.27 (0.44)	0.45 (0.50)	0.00 (0.00)
Total	1.73 (2.80)	2.81 (2.44)	0.15 (0.67)

Severity of rigidity was not associated with any of the selected gait parameters.

Cerebrovascular disease (β=.20, p<.01) was associated with bradykinesia severity, RBANS total score (β=−.15, p<.05), and depression (β=.14, p<.05). Cardiovascular disease (β=.15, p<.05) and depression (β=.16, p<.05) were associated with rigidity severity. The presence of osteoarthritis and cardiovascular risk factors were not related to bradykinesia or rigidity.

Further, we examined the relationship of MPS with location of bradykinesia (axial or peripheral). The presence of axial bradykinesia was associated with velocity (β=−.25, p<.01), stride length (β=−.23, p<.01), COV stride length (β=.16, p<.01), and COV swing time (β=.16, p<.01). Bradykinesia in limbs was not associated with any of the quantitative gait parameters.

Discussion

This study reveals that rigidity and bradykinesia were the most common MPS in our sample of community-residing non-demented older adults. The main finding was that presence of bradykinesia, particularly axial, was related to worse performance on spatial- and variability-related gait parameters, regardless of the presence of clinical gait abnormality. To the best of our knowledge, this is the first study to investigate the association between MPS and quantitative gait parameters in normal aging.

MPS and especially bradykinesia have been related to spatial and variability parameters of gait in older adults. Furthermore, bradykinesia has been associated with stride time variability during "on" but not "off" state," which suggests an association with levodopa integrity (Schaafsma et al. 2003). Concerning the dopaminergic pathway, both bradykinesia and PIGD have been associated with [^{123}I]β-CIT SPECT binding in patients with PD (Pirker 2003). Additionally, gait akinesia in PD was mainly attributed to an inability to increase step length (Morris et al. 1994). Interestingly, by comparing Alzheimer's disease patients with increased MPS and those with decreased MPS, Camicioli et al. have previously shown that patients with more MPS showed impaired spatial and variability gait parameters (2006). Regardless of the cause of MPS, changes in axial function, including axial bradykinesia, were associated with the need for assistive walking devices in older adults without PD (Louis et al. 2006). Taken together, the presence of axial bradykinesia likely represents a key element of MPS responsible for abnormal gait performance in normal aging. In addition, the similarity of the present investigation, linking bradykinesia and quantitative gait parameters, with previous PD studies (Morris et al. 1994; Schaafsma et al. 2003) suggests a deficit in the nigral pathway. In support, a recent clinicopathological study reported that nigral neuronal loss was associated with the presence of MPS in aging (Buchman et al. 2012). However, the etiopathogenesis of MPS in aging is unclear and seems multifactorial: early features of neurodegenerative disorders like dementia with Lewy bodies or Alzheimer's disease, clinical expression of vascular infarcts, or

Table 3 Association between individual MPS and quantitative gait parameters

	Gait velocity	Stride width	Stride length	Swing time	COV stride length	6. COV swing time
Bradykinesia	−.17 (−3.06, −.83)*	.20 (.19, .63)*	−.23 (−3.21,−1.41)*	−.08 (−.01, .00)	.27 (.15, .36)*	.17 (.08, .38)*
Rigidity	−.05 (−1.50, .53)	−.01 (−.22, .18)	−.09 (−1.59, .08)	.02 (−.01, .00)	−.01 (−.11, .08)	−.02 (−.11, .16)

Estimate (95 % CI)

COV coefficient of variability adjusted for age, gender, education level, clinical gait abnormality, medical illness index score, and physical activity level

*p≤0.004 (survives Bonferroni correction)

physiological signs of an age-related decline in dopaminergic neurons (Louis and Bennett 2007). Clearly, this association between axial bradykinesia and quantitative gait parameters should be studied in a prospective design study to determine whether it represents an early sign of a neurological disease.

The secondary objective of this study focused on the pathogenesis of MPS in normal aging. Neurodegenerative diseases (e.g., PD) and vascular lesions involving the basal ganglia can cause MPS in the elderly (Louis and Bennett 2007). In the current study, we confirm lower cognitive scores as well as higher prevalence of cerebrovascular disease and cardiovascular risk factors in individuals with MPS. Regarding individual MPS, cerebrovascular disease, cognitive function, and depression were associated with bradykinesia in the current study. Rigidity was not associated with cerebrovascular, but was associated with cardiovascular disease. Interestingly, the observation that no MPS was associated with vascular risk factors in our study highlights the complex interaction between vascular risk factors, MPS, and white matter disease. In a previous study conducted in community-residing older adults with abnormal gait, stroke, diabetes, and depression were associated with the presence of parkinsonian gait (Ambrose et al. 2006). Concerning the relationship between cerebrovascular disease and MPS, an increased risk of MPS in individuals with lacunar infarcts was due to bradykinesia (de Laat et al. 2012). Furthermore, in a pathological study examining the prevalence of neurological signs in vascular dementia, the authors revealed that bradykinesia was seen in all patients (Staekenborg et al. 2008), confirming the close link between cerebrovascular disease and bradykinesia. The association between cardiovascular disease and rigidity suggests an alternative mechanism, possibly related to cerebral oxygenation. However, longitudinal studies are needed to address the relationship between MPS and vascular risk factors.

Global cognitive functioning was associated with bradykinesia in our sample. In early stages of PD, bradykinesia has been correlated with working memory and executive functioning, whereas rigidity and tremor were not correlated with any cognitive measures (Domellof et al. 2011). Fleischman et al. (2005) found no specific relationship between MPS and cognitive performance in a cohort of older adults without PD. As previously stated, several studies have already demonstrated an association between MPS and cognitive deficits in aging (Richards et al. 1993; Louis et al. 2004, 2005a, 2010; Boyle et al. 2005). As the present study aimed to determine the association between MPS and quantitative gait parameters, we did not further examine the relationship of individual MPS and cognition. In terms of depression, GDS scores were associated with both bradykinesia and rigidity, a finding in line with prior results (Uemura et al. 2013).

This study is not without its limitations. The UPDRS was designed to evaluate motor impairment in patients with PD. However, no such scales are available to determine the presence of MPS in healthy older adults. In an effort to identify markers of abnormal motor aging at very early stages, we took a sensitive approach to define MPS based on the presence of any one domain, but more stringent methods have been employed (Louis et al. 2004, 2005b). While this study is the first to demonstrate the association between MPS and quantitative gait parameters in aging, the cross-sectional design does not afford causal inferences. Future prospective studies should be conducted to examine whether MPS precedes gait disturbances.

In conclusion, bradykinesia, particularly axial bradykinesia, was strongly associated with poor walking performance in older individuals without idiopathic PD. Specifically, bradykinesia affects the spatial components of gait as well as the control of regularity of gait. Bradykinesia was also associated with cerebrovascular disease in our sample. Based on these findings, clinicians should consider assessing older adults presenting with bradykinesia not only for gait disorders but also for cerebrovascular disease, depressive symptoms, and cognitive impairments.

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Conflict of interests The authors have no competing interests to report.

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