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PERIPHERAL NEUROPATHY IS ASSOCIATED WITH MORE FREQUENT FALLS IN PARKINSON'S DISEASE

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Abstract

Introduction—Peripheral neuropathy is a common condition in the elderly that can affect balance and gait. Postural imbalance and gait difficulties in Parkinson's disease (PD), therefore, may stem not only from the primary neurodegenerative process but also from age-related medical comorbidities. Elucidation of the effects of peripheral neuropathy on these difficulties in PD is important to provide more targeted and effective therapy. The purpose of this study was to investigate the association between lower-limb peripheral neuropathy and falls and gait performance in PD while accounting for disease-specific factors.

Methods—From a total of 140 individuals with PD, 14 male participants met the criteria for peripheral neuropathy and were matched 1:1 for Hoehn & Yahr stage and duration of disease with 14 male participants without peripheral neuropathy. All participants underwent fall (retrospectively) and gait assessment, a clinical evaluation, and [^{11}C]dihydrotetrabenazine and [^{11}C]methylpiperidin-4-yl propionate PET imaging to assess dopaminergic and cholinergic denervation, respectively.

Results—The presence of peripheral neuropathy was significantly associated with more falls (50% vs. 14%, p=0.043), as well as a shorter stride length (p=0.011) and greater stride length

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AUTHORS' CONTRIBUTIONS

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variability (p=0.004), which resulted in slower gait speed (p=0.016) during level walking. There was no significant difference in nigrostriatal dopaminergic denervation, cortical and thalamic cholinergic denervation, and MDS-UPDRS motor examination scores between groups.

Conclusion—Lower-limb peripheral neuropathy is significantly associated with more falls and gait difficulties in PD. Thus, treating such neuropathy may reduce falls and/or improve gait performance in PD.

Keywords

Neuropathy; Fall; Gait; Parkinson's disease

INTRODUCTION

In individuals with Parkinson's disease (PD), dopaminergic medication-refractory axial motor symptoms represent significant causes of disability, and result in loss of independence in performing activities of daily living and a reduced quality of life [1,2]. Gait and balance difficulties represent a major clinical challenge in PD that are in urgent need of effective therapies.

Effective treatments depend on the accurate identification of the risk factors underlying axial motor impairments in PD. Although gait and balance problems stem, in part, from the primary neurodegenerative process of PD [3,4], disease-independent contributing factors may also exist. In fact, neuromuscular factors such as decreased peripheral sensation, hip strength, and ankle proprioception have been linked to gait and balance difficulties, as well as falls in otherwise healthy older adults [5–8]. Specifically, older adults with peripheral neuropathy have been found to have impaired balance and decreased ankle proprioception compared to those without neuropathy [7]. Decreased peripheral sensation has also been identified as a risk factor for falling in older adults [6,8]. Furthermore, elderly fallers with peripheral neuropathy have a more variable gait pattern compared to elderly non-fallers with peripheral neuropathy [5]. Given that the prevalence of peripheral neuropathy in the older adult population has been reported to be approximately 15% [9], it is likely also a contributing factor to gait and balance problems in an age-related condition like PD.

The purpose of this study was to investigate the association between lower-limb peripheral neuropathy and fall history and gait performance in PD. The hypothesis was that the presence of peripheral neuropathy would be significantly associated with a higher fall history frequency and impaired gait performance, independent from PD-specific factors. If confirmed, peripheral neuropathy could be further examined as a distinct target for the management of axial motor impairment amongst PD patients. Hence, gait and balance difficulties may further improve by addressing disease-independent contributing factors such as peripheral neuropathy, in addition to the use of therapies targeting the primary neurodegenerative processes of PD.

METHODS

Participants

This case-control study included a total of 28 participants (all males) who were part of a larger study of 140 individuals with PD. Of the larger cohort, 14 participants met the criteria for lower-limb peripheral neuropathy (10.0% prevalence; 95% CI: 5.0–15.0%) and were matched 1:1 for modified Hoehn & Yahr stage (± 0.5) and duration of disease (± 5.0 years) with 14 controls (PD; no peripheral neuropathy). Demographic and clinical data for both groups and the larger cohort are presented in Table 1. All patients met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [10]. The diagnosis of PD was consistent with the presence of a pattern of nigrostriatal dopaminergic denervation typical of PD with vesicular monoaminergic transporter-type 2 (VMAT2) positron emission tomography (PET) [11].

This study was approved by the University of Michigan Medical School Institutional Review Board for human studies. All participants gave their written informed consent prior to study procedures.

Definition of Lower-Limb Peripheral Neuropathy

Lower-limb peripheral neuropathy was defined as the presence of three criteria: (1) high vibration perception threshold (VPT) at the medial malleoli; (2) abnormal temperature sensation at distal shanks; and (3) absence of ankle jerk reflexes. The three criteria for the control group were (1) normal VPT; (2) no detection of a temperature gradient indicating normal temperature perception; and (3) presence of ankle jerk reflexes.

VPT was measured at the right and left medial malleoli with a hand-held biothesiometer (Bio-Medical Instrument Co., Newbury, OH, USA). The device produces vibrations at a frequency of 100 Hz and of amplitudes ranging from 0–50. This scale reflects the applied voltage, which is proportional to the square root of the vibration amplitude. To determine VPT, the plastic vibrating element of the biothesiometer was placed horizontally, directly on the participant's skin. The amplitude was slowly increased until the participant's first sensation of the vibration. All VPT data were collected by the same laboratory technician. Three trials were completed bilaterally. The VPT was quantified as the average of all six trials. A high VPT value was defined as a value greater than the sex- and age-specific 95^{th} percentile established by Wiles et al. [12]. A normal value was defined as a value smaller than the sex- and age-specific 90^{th} percentile [12].

Temperature perception was measured on the lateral portion of the right and left shanks. A cold metal tool was applied against the participant's skin and moved from the ankle to the knee by an experienced neurologist. The participant was asked whether they sensed a cold gradient (i.e., whether they perceived a different in temperature of the tool on their skin from distal to proximal shank). Temperature perception was quantified in a binary manner as either abnormal (presence of a cold gradient sensation as indicated by the participant) or normal (absence of a cold gradient sensation as indicated by the participant). The presence of abnormal and normal temperature perception as a criterion for peripheral neuropathy was defined as the presence or absence of the cold gradient bilaterally, respectively.

Ankle jerk reflex was assessed bilaterally by an experienced neurologist. This reflex was scored on a scale from 0 to 3 as absent (0), mild (1), normal (2), or brisk (3). Participants met the third criterion for peripheral neuropathy if they had an absence (0) of ankle jerk reflexes bilaterally. A participant met the criterion for the control group if they had mild to brisk (1–3) ankle jerk reflexes bilaterally.

Clinical Assessment

The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was performed by an experienced neurologist the morning after the participants withheld their dopaminergic medications overnight, and thus in the dopaminergic "off" state. The motor examination score (part III of the MDS-UPDRS) was calculated.

Fall Assessment

To assess whether the participants had a history of falls, they were asked if they were falling. A fall was defined as an unexpected even during which a person falls to the ground, unrelated to freezing of gait or loss/near loss of consciousness (e.g., due to symptomatic orthostatic hypotension). Also, isolated falls due to trips or slips and near falls were not included. The participants without a history of falls were given a score of 0 and those with a history of falls were given a score of 1. Fallers were categorized into one of four groups based on the frequency of their falls (1=rarely; 2=occasionally (less than once per day); 3=approximately once per day; 4=more than once per day).

Gait Assessment

All participants underwent a gait assessment in the dopaminergic "off" state (as defined above). Each participant performed two walking trials on an 8-meter pressure mapping walkway (GAITRite®, Franklin, NJ, USA) wearing their own flat shoes (no heels). They were instructed to walk at their normal walking speed, starting and finishing about 1.5–2 meters before and after the walkway, respectively. Several spatiotemporal parameters (speed, stride length, and stride length coefficient of variation, stride time, and stride time coefficient of variation) were extracted from each trial, height-normalized (speed and stride length only), and averaged across trials.

Imaging

All participants underwent MRI, [^{11}C]dihydrotetrabenazine ([^{11}C]DTBZ) vesicular monoamine transporter type 2 (VMAT2) PET, and [^{11}C]methylpiperidin-4-yl propionate (an acetylcholinesterase ligand; [^{11}C]PMP) PET imaging of the brain. The PET scans were performed in three-dimensional imaging mode with an ECAT Exact HR + tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN, USA), as previously reported [11,13]. The [^{11}C]DTBZ dynamic scan was performed the morning after the participants withheld their dopaminergic medications overnight. MRI was performed on a 3T Philips Achieva system (Philips, Best, The Netherlands). A standard T1-weighted series of a 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane.

Motion-corrected PET image frames were spatially co-registered to the MR images using standard co-registration procedures. The volume of interest (VOI) included the caudate nucleus and putamen of each hemisphere and were manually traced on the MR images. Time activity curves for each VOI were generated from the spatially aligned PET frames. [^{11}C]DTBZ VMAT2 distribution volume ratio (DVR) was then estimated, as previously reported [14]. Cortical and thalamic [^{11}C]PMP acetylcholinesterase hydrolysis rates per minutes (k_3), a measure of cholinergic activity, were also estimated [15].

Statistical Analysis

To compare demographic and clinical data between groups, a series of one-way analyses of variance (ANOVA) and Pearson Chi-Square (X^2) analyses were used for the continuous and binary dependent variables, respectively. Given that no demographic or clinical differences were found between groups (Table 1), the hypothesis-driven analyses did not require to account for these parameters. Therefore, a second series of ANOVA and Pearson Chi-Square analyses were performed to determine whether gait performance and fall history and frequency differed between groups. The dependent variables of interest were height-normalized gait speed, height-normalized stride length, stride length coefficient of variation, stride time, stride time coefficient of variation, and fall history. An alpha level below 0.05 indicated statistical significance. Correction for multiple statistical analyses was performed on the second series of analyses only using the Benjamini-Hochberg procedure.

RESULTS

The group of participants with lower-limb peripheral neuropathy did not significantly differ from those without peripheral neuropathy in terms of sex, age, body mass index, modified Hoehn & Yahr stage, MDS-UPDRS motor examination score, duration of disease, levodopa equivalent daily dose, striatal dopaminergic innervation, or cortical and thalamic cholinergic innervation (Table 1). Three participants had a history of diabetes (all: 3/28, 11%; cases: 3/14, 21%; controls: 0/14, 0%); the proportion of those with such a history did not differ significantly between groups (Table 1). Most participants were on dopaminergic replacement therapy (all: 26/28, 93%; cases: 13/14, 93%; controls: 13/14, 93%; $p > 0.05$).

Fall history and frequency and gait data are presented in Table 2. The presence of lower-limb peripheral neuropathy was significantly associated with a higher frequency of fallers ($p = 0.033$; Table 2); half (50%) of the participants with peripheral neuropathy had a history of falling in comparison with the control group, for which only 14% reported falling ($p = 0.043$; Table 2). Of the fallers, 29% of those with peripheral neuropathy occasionally experienced a fall and 71% rarely experienced a fall; meanwhile all (100%) those in the control group reported falling rarely. The presence of peripheral neuropathy was also significantly associated with a slower gait speed, a shorter stride length and greater stride length variability (Table 2). Conversely, peripheral neuropathy did not predict stride time or stride time variability (Table 2).

DISCUSSION

The present work investigated the association between lower-limb peripheral neuropathy and falls and gait performance in PD. Results indicate that the presence of peripheral neuropathy was significantly associated with a higher frequency of history of falls and impaired gait performance; hence our hypothesis was accepted. Similar findings have been reported in the literature in non-PD elderly populations in which the presence of peripheral neuropathy has been linked repeatedly to impaired balance [16,17] and falls [5,8,18] in older adults.

Lower-limb peripheral neuropathy was significantly associated with a slower gait speed and a more variable and shorter stride length during normal pace walking. This latter factor, a shorter stride length, is what most likely produced the slower walking speed in the case participants given that no significant associations were found between peripheral neuropathy and stride time. In other words, the participants with peripheral neuropathy walked slower due to a shorter stride and not a slower stride. Similar findings have been reported in adults with peripheral neuropathy but without PD [19]. Mueller et al. [19] reported that these elderly individuals with neuropathy walked slower and walked with a shorter stride length than those without peripheral neuropathy. Interestingly, the neuropathy patients also employed a different walking strategy that involved a hip-dominant strategy during push-off as opposed to an ankle-dominant strategy for which the plantar flexors are used to propel the leg and center of mass forward, as typically seen in a normal healthy population [19]. It is unknown, however, whether the PD patients in the current study also utilized this hip-dominant gait strategy during push-off. These data were not collected.

The significant associations between the presence of peripheral neuropathy and a higher fall history frequency and impaired gait performance in PD in our study cannot be explained by disease-specific factors, age, or other clinical factors. Not only were groups matched 1:1 for disease state and duration (Table 1), but our definition of peripheral neuropathy was also based on age-specific normative data for vibration perception threshold from 1365 normal subjects [12]. Our findings cannot be explained by PD-specific factors as no significant differences existed in the degree of nigrostriatal dopaminergic denervation, cortical and thalamic cholinergic denervations, and levodopa equivalent daily dose between groups (Table 1). Given that such dopaminergic denervation and cholinergic denervation have been linked to impaired gait [3,4] and postural sensory integration [20], a lack of group differences in these parameters in our study suggests that peripheral neuropathy is a true risk factor for falls and impaired gait in PD. Levodopa equivalent daily dose is also of relevance as lifetime exposure to dopaminergic drugs has been reported to be positively correlated with peripheral neuropathy [21]. It is possible that such dopaminergic therapy led to the development of peripheral neuropathy in our cohort, especially that lifetime exposure to these drugs was not investigated. Only current doses were considered. However, participants with and without lower-limb peripheral neuropathy reported similar levodopa doses, as well as similar disease duration and severity. It is unlikely, therefore, that dopaminergic drugs would have affected each group differently. Regardless of the cause of peripheral neuropathy, our conclusion that it is a risk factor for falls and impaired gait in PD holds. Although more cases reported a history of diabetes than controls (21% vs. 0%), this group

difference was not significant, and thus could not account for the significant associations between peripheral neuropathy and falls and gait difficulties.

Findings of this study reveal that lower-limb peripheral neuropathy is a significant contributing factor to fall risk in PD, thus expanding the list of potential causes of falls in this population. Several possible mechanistic factors underlying fall risk have been identified previously ranging from primary neurodegenerative processes of PD to cardiovascular factors [22,23]. For instance, lower thalamic cholinergic activity has been associated with increased fall risk in PD [13]. Falls have also been linked to dementia [24] and indirectly to β-amyloid deposition in PD [23]. Collectively, these observations underscore the multifactorial etiology of falls in PD, including not only extra-striatal PD-related factors but also age-associated medical comorbidities.

Results from this study suggest that clinicians and researchers alike should evaluate and consider peripheral neuropathy when assessing patients with PD, especially with regard to motor impairments such as gait and balance difficulties. Axial motor difficulties in PD may potentially be improved by treating peripheral neuropathy specifically with relatively simple techniques (e.g., physical therapy, tactile or vibratory feedback techniques) that could be complementary to the regular antiparkinsonian treatment. Such techniques could be particularly important in PD patients with peripheral neuropathy if the neuropathy is the driving factor behind these motor impairments, especially given the unresponsiveness of gait and balance problems to dopaminergic pharmacotherapy in PD [25]. In fact, screening for lower-limb peripheral neuropathy in PD patients, regardless of whether gait and balance difficulties are present, is warranted. Relatively simple techniques could target peripheral neuropathy and potentially delay or even prevent the development of these motor impairments. Increasing evidence supports physical therapy, exercise, and monochromatic infrared photo energy, among others, as effective therapies for the complications of peripheral neuropathy [26,27]. For instance, a simple 6-week home exercise program improved muscle function and quality of life in a population with peripheral neuropathy [27]. In addition, treatment that included neuromuscular re-education, balance and strength training, stretching exercises, and infrared photo energy revealed improvements in lower extremity sensation and balance, resulting in a decrease in falls. Lastly, monochromatic infrared photo energy therapy alone also showed improvements in foot sensation in individuals with peripheral neuropathy [26]. Hence, considering and evaluating PD-independent contributing factors to balance and gait impairments, such as peripheral neuropathy, may potentially lead to better outcomes for PD patients via targeted therapies. Clinical evaluation and treatment of underlying causes of neuropathy, such as diabetes, vitamin B12 deficiency, or alcohol abuse, may also help to potentially reverse or alleviate the neuropathic process.

The present study was not without limitations. First, we utilized a cross-sectional design, which does not allow for cause-and-effect relations to be established, but rather associations between factors. Second, our sample size of 28 participants was small and consisted of males only. However, meticulous case-control matching on several critical factors was used, thus greatly reducing the likelihood that group differences were due to other contributing factors. Also, our small sample size was partly due to a very strict definition of peripheral

neuropathy, which we consider a strength of our study. This strict definition may explain why the prevalence of lower-limb peripheral neuropathy reported herein (10%) is lower than the 15% rate previously reported for older adults [9]. The participant of the current study had to meet three criteria involving both left and right lower limbs; meanwhile Gregg et al. [9] defined peripheral neuropathy as at least one area under either foot with impaired sensation. The nature of our larger cohort partly explains our male-only sample. Women only made up 25% of the cohort, which is due to the skewed male-to-female prevalence ratio of PD [28] and to our male-dominant recruitment pool (e.g., United States Department of Veterans Affairs). Moreover, only three women met the vibration perception threshold criterion, which was sex and age specific, none of which met both of the other two criteria for lower-limb peripheral neuropathy. Third, we matched for Hoehn and Yahr stage between the two groups. Given that the Hoehn and Yahr staging system is mainly driven by postural imbalance, our analysis was limited in assessing for postural changes between the groups. Fourth, our assessment of lower-limb peripheral neuropathy had its flaws. It did not include a nerve conduction study or electromyography—the gold standard for non-invasive nerve function evaluation—given that we performed a retrospective analysis. Including this evaluation may have better identified those patients with peripheral neuropathy. Furthermore, temperature perception was assessed with a cold metal tool, which had the potential to warm up during the evaluation. Since the tool was in contact with the participant's skin for short periods of time (i.e., foot to knee), warming up of the instrument was limited. Regardless, if warming up did occur, our findings would represent a conservative assessment of neuropathy since the instrument was moved distal to proximal (foot to knee) and abnormal temperature perception was defined as the proximal site being perceived as colder than the distal site. Last, our fall assessment was retrospective; therefore, the data relied on the participants' accurate recollection of past falls. Given the retrospective nature of this study, a prospective assessment of falls was not available. We did provide each participant, however, with a detailed definition of a fall and addressed any ambiguity to ensure proper fall categorization.

We conclude that lower-limb peripheral neuropathy was found to be significantly associated with a higher frequency of history of falling and more gait difficulties in individuals with PD, independent from age, Hoehn & Yahr stage, duration of disease, nigrostriatal dopaminergic denervation, and cortical and thalamic cholinergic denervations. This important contributing factor to falls and gait performance should be considered and evaluated by clinicians and researchers when assessing PD patients for axial motor impairments. These impairments may potentially be improved or even prevented by treating lower-limb peripheral neuropathy with simple, cost-effective targeted techniques.

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HIGHLIGHTS

- Lower-limb peripheral neuropathy is associated with more falls in PD
- Lower-limb peripheral neuropathy is also associated with gait difficulties in PD
- These effects are independent from several PD-specific factors and diabetes
- Fall prevention strategies for PD patients should consider peripheral neuropathy
- Evaluation of lower-limb peripheral neuropathy is important in PD

Table 1

Demographic and clinical data (average ± standard deviation) of larger cohort, cases, and controls, as well as statistics of case-control comparisons.

Dependent Variables	Mean ± Standard Deviation			F/X^2 value [a]	p value [b]
	Larger Cohort	Cases (PD w/PN)	Controls (PD w/o PN)		
Sex (M/F)	105/35	14/0	14/0	N/A	N/A
Age (years)	65.5 ± 7.3	67.9 ± 7.2	64.8 ± 8.1	1.124	0.299
Body mass index (kg/m^2)	28.4 ± 5.0	29.2 ± 5.2	27.3 ± 4.4	1.118	0.300
Modified Hoehn & Yahr stage	2.4 ± 0.5	2.4 ± 0.6	2.3 ± 0.5	0.744	0.396
MDS-UPDRS motor score	31.9 ± 14.0	38.5 ± 17.2	28.6 ± 12.7	2.994	0.095
Duration of disease (years)	5.8 ± 4.0	6.4 ± 4.9	6.9 ± 3.7	0.093	0.763
Levodopa equivalent daily dose	652.7 ± 501.6	757.6 ± 509.5	852.1 ± 828.7	0.132	0.719
History of diabetes (yes/no)	10/130 (7%)	3/11 (21%)	0/14 (0%)	3.360	0.067
Nigrostriatal dopaminergic innervation[c]	1.96 ± 0.31	1.98 ± 0.39	2.03 ± 0.41	0.124	0.728
Cortical cholinergic innervation[d]	0.0237 ± 0.0028	0.0249 ± 0.0043	0.0240 ± 0.0030	0.340	0.565
Thalamic cholinergic innervation[d]	0.0547 ± 0.0055	0.0561 ± 0.0062	0.0522 ± 0.0056	3.016	0.094

[a] X^2 values calculated for the binary variables ‘sex’ and ‘history of diabetes’.

[b] Value for case-control comparisons.

[c] [^{11}C]DTBZ VMAT2 distribution volume ratio.

[d] [^{11}C]PMP k_3 (/min).

PD: Parkinson’s disease; PN: peripheral neuropathy; MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale.

Table 2

Comparisons of fall and gait data (average ± standard deviation) between cases and controls.

Dependent Variables	Mean ± Standard Deviation		F/X^2 value [a]	p value
	Cases PD w/PN	Controls PD w/o PN		
History of falls (yes/no)	7/7 (50%)	2/12 (14%)	4.452	0.043[b]
History of falls (0–4 scale)	0.6 ± 0.7	0.1 ± 0.4	5.096	0.033[b]
Gait speed (% height/s)	55.4 ± 11.0	66.0 ± 10.8	6.639	0.016[b]
Stride length (% height)	63.1 ± 10.9	73.0 ± 8.2	7.453	0.011[b]
Stride length variability (CoV)	4.0 ± 1.6	2.5 ± 0.6	10.241	0.004[b]
Stride time (s)	1.1 ± 0.1	1.1 ± 0.1	0.540	0.469
Stride time variability (CoV)	3.8 ± 3.7	2.9 ± 2.2	0.711	0.407

[a] X^2 value calculated for the binary variable ‘history of falls’.

[b] Statistically significant after correcting for multiple comparisons using the Benjamini-Hochberg procedure.

PD: Parkinson’s disease; PN: peripheral neuropathy; CoV: coefficient of variation.