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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 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.

1. 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.

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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.

2. Methods

2.1. 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.

2.2. 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 to 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 95th percentile established by Wiles et al. [12]. A normal value was defined as a value smaller than the sex- and age-specific 90th 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.

2.3. 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.

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

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

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