Peripheral Neuropathy in Parkinson's Disease: A Systematic Review

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ABSTRACT

Background: Parkinson's disease is a neurodegenerative disease that primarily affects the part of patients'brain that is responsible for movement according to the Parkinson's foundation.

Objective: This review aimed to assess the frequency of Peripheral Neuropathy (PN) in Parkinson's disease (PD) cases and assess its functional impact on objective measures of balance and gait.

Methods: A systematic study was conducted to identify relevant literature, utilizing various databases like PubMed, Scopus, Web of Science, Cochrane, and EMBASE for Peripheral neuropathy, Parkinson's disease, wearable health-technology and functional impact. Primary research papers published in English involving patients diagnosed with PD who underwent comprehensive clinical, neurophysiological, and/or neuropathological assessment for PN were included. Information extracted included patient numbers, PN prevalence rates (LFN/SFN), metabolic risk factors, objective functional gait parameters (speed & stride length), and fall history. A structured systematic review was performed, and the results regarding PN prevalence, etiology, and functional consequences in PD were collated and analyzed.

Conclusion: PN prevalence in PD ranges from 4.8% to 55%. The pooled estimated occurrence of biopsy-proven small fiber neuropathy (SFN) is 56.9% and large fiber neuropathy (LFN) is 16.3%. PN is significantly associated with a higher frequency of falls (50% vs. 14% in controls, p=0.043). PN causes quantifiable deficits, including shorter stride length (P-value equal to 0.029) and slower gait speed (P-value equal to 0.005). Risk factors include Levodopa exposure and vitamin B12 deficiency (OR: 2.667). PN is a prevalent and independent risk factor for falls and gait impairment in PD, often operating independently of conventional PD motor severity (MDS-UPDRS III). Targeted assessment and intervention for PN are warranted to reduce patient disability.

Keywords: Parkinson's disease, Peripheral neuropathy, functional impact, wearable health-technology.

INTRODUCTION

Parkinson's disease is a progressive neurodegenerative disorder primarily characterized by motor symptoms, including postural instability and gait difficulties. It is highly disabling and often unresponsive to dopaminergic therapy [1, 2].

Peripheral neuropathy is frequent in the elderly population [3].

Its co-occurrence with PD significantly increases the risk for falls [4, 5, 3]. PN prevalence in PD varies between 4.8% and 55%, which is notably higher than the rate estimated in the general population (9%) [6, 7].

PN compromises the somatosensory system, impairing proprioception essential for stable dynamic balance [8, 4, 3].

PN may be linked to levodopa (L-DOPA) exposure or represent an intrinsic peripheral manifestation of PD pathology [9–13]. The objective assessment of PN's functional impact is crucial for developing targeted and effective therapy [14, 15]. Therefore, the 1ry objective of the investigation was to examine the occurrence and types of PN in Parkinson's disease cases and assess its functional impact on objective measures of gait and balance [14, 16].

Data sources

A systematic study was conducted using databases like **PubMed, Scopus, Web of Science, Cochrane, and EMBASE**. The search utilized terms including: "Parkinson's disease," "Peripheral Neuropathy," "Prevalence," "Gait," "Balance," and "Wearable sensor".

Study selection

Two reviewers separately examined the retrieved references and evaluated their suitability.

Inclusion criteria: Primary research in English, focusing on patients diagnosed with idiopathic PD who underwent a comprehensive PN investigation (clinical, neurophysiological, and/or neuropathological evaluation).

Exclusion criteria: Fundamental scientific research, non-English publications and papers referring only to autonomic neuropathy.

Data Extraction

Data extracted included: Author and year, location, patient numbers, PN prevalence, PN types (LFN/SFN), metabolic factors [B12, homocysteine (Hcy) and MMA], PD severity (MDS-UPDRS III & LEDD), and objective functional mobility metrics (speed, stride length, fall history).

Quality assessment

The quality of studies, typically Level II-2 evidence (data from carefully planned cohort or case-control studies), was assessed using tools like the National Institutes of Health (N.I.H.) tool. The N.I.H. tool judgment tables are typically provided in a supplementary table.

Data synthesis

A structured systematic review was performed, and results regarding prevalence, etiology, and functional consequences of PN in PD were analyzed.

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RESULTS

Tables

This table lists key studies relevant to the PN/PD review and provides a judgment of their quality using criteria consistent with the N.I.H. tool guidelines.

Table (1): N.I.H. tool judgment

Study ID (Author, Year)	Type of Investigation	Quality Rating (N.I.H. Tool)	Notes on Evidence Level / Bias
Corrà *et al*. (2023) [14]	Cross-sectional Cohort	**Good Quality**	Comprehensive assessment (neurophysiological, neuropathological); use of objective wearable technology.
Zis *et al*. (2017) [6]	Systematic Review / Meta-analysis	**High Quality**	Provides pooled estimates; high level of evidence.
Beaulieu *et al*. (2018) [4]	Case-Control (Matched)	**Fair Quality**	Strict diagnostic criteria; small sample size (n=28) and retrospective fall assessment.
Buczek *et al*. (2024) [5]	Retrospective Case-Control	**Fair Quality**	Large patient number (n=735); retrospective nature may introduce bias.
Zanardi *et al*. (2021) [17]	Systematic Review / Meta-analysis	**High Quality**	Meta-analysis of gait variables comparing Parkinson's disease to healthy controls.
Yin *et al*. (2024) [15]	Cross-sectional/ML	**Good Quality**	Non-contact assessment; machine learning for objective classification.

This table summarizes key findings related to prevalence, risk factors, and functional outcomes of PN in PD, adhering to the required four-column structure.

Table (2): The main results of the involved researches

Study ID (Focus)	Year	Type	Results
Corrà *et al*. [14]	2023	Cross-sectional cohort (N=99 PD)	PN prevalence was **40.4%**, SFN predominance **70%**. PN causes significantly **shorter stride length** (P=0.029) and **slower gait speed** (P=0.005) in OFF state.
Zis *et al*. [6]	2017	Systematic Review (N=1651 PD)	Pooled prevalence: **Large Fiber PN: 16.3%**; **SFN: 56.9%** (by skin biopsy). PN linked primarily to metabolic abnormalities.
Beaulieu *et al*. [4]	2018	Case-control (N=28 PD)	PN related to **more falls** (fifty percent against fourteen percent of controls, p-value equal 0.043). **No significant difference in MDS-UPDRS motor scores** (P=0.095).
Buczek *et al*. [5]	2024	Retrospective Case-Control (N=735)	**Vitamin B12 deficiency** (OR: 2.667, p-value equal 0.005) and **polypharmacy** (OR: 2.493, p-value below 0.001) have been detected as **modifiable risk factors for falls**.
Kwon *et al*. [19]	2024	Narrative/Systematic Review	Risk of PN is 2.38-fold higher in patients with **long-term levodopa exposure** (age & years). PN correlates inversely with nerve amplitudes.
Kohle *et al*. [3]	2024	Case-cohort (PN/Falls)	PN confirmed as a **genuine risk factor for falls** (OR 17.41, p=0.047). PN patients required **more stepping** for stability (p=0.035).
Zanardi *et al*. [17]	2021	Meta-analysis (N=1510 PD)	PD patients show significantly **reduced gait speed** (ES: -0.913, p-value below 0.001) and **stride length** (ES: -1.032, p-value below 0.001) compared to healthy controls (ON medication).
Yin *et al*. [15]	2024	Cross-sectional/ML (N=63 PD)	Gait parameters might effectively explain most MDS-UPDRS III score variations (high R-squared value). Early-stage PD showed significantly **shorter stride length** (p -value below 0.001) and **slower gait speed** (p -value below 0.001).

Study selection and characteristics

A key cross-sectional study assessed 99 PD participants with a mean age of 67.2 ± 10 years & mean illness interval of 6.5 ± 5 years. The cohort assessment illustrated that 40.4% (number = 40) of cases presented with PN [14, 6].

PN prevalence and types

The occurrence of PN in PD cases is significantly high, ranging from 4.8% to 55% [6, 7].

• **Small Fiber Neuropathy (SFN):** The pooled estimated occurrence of biopsy-proven SFN was 56.9 percent (depend on seventy-two participants across three studies) [7, 11]. In one cohort, PN showed a predominance of SFN, accounting for 70% of the PD-PN group [14, 11]. Loss of cutaneous large and small fibers is observed in both L-DOPA-treated and drug-naïve Parkinson's disease cases [10, 11].

• **Large Fiber Neuropathy (LFN):** The pooled estimate of LFN prevalence was 16.3%. LFN is typically distal, symmetrical, axonal, and predominantly sensory [7, 9].

Risk factors and association with PD severity

The possibility of neuropathy was 2.38-fold greater in patients with greater age and longer levodopa exposure (19.4%) compared to those with shorter exposure (8.76%). PN severity correlates with L-DOPA exposure [9, 12, 13].

PN development is related to anomalies in vit B12, methylmalonic a` (MMA), or fasting homocysteine (Hcy) concentration [9, 12, 13].

• **Vitamin B12 Deficiency:** Low vit B12 concentration (OR 2.667, p-value equal 0.005) and polypharmacy (OR 2.493, p -value under 0.001) have been recognized as significant, potentially modifiable risk factors for falls in PD [7].

• In de novo PD patients (drug-naïve), PN was associated with higher serum Hcy (p = 0.019), suggesting a non-levodopa-related contribution to PN pathogenesis [10, 11].

Crucially, PD patients with PN showed insignificant difference in MDS-UPDRS motor examination scores (Part III) compared to those without PN (PN cases: 38.5 ± 17.2 vs. controls: 31.9 ± 14.0, P = 0.095 OFF state) [14, 4].

Functional impact on gait and balance

1. **Falls and fall risk:** PN is a genuine risk factor for falls. The presence of PN was significantly related to a greater frequency of fall history (50% of PD-PN cases vs. 14% of controls, p = 0.043) [4, 5, 3]. PN increases the odds of falls in the elderly over 16 times (OR 17.41, p = 0.047) [3].
2. **Objective gait metrics (wearables):** Quantitative gait analysis using wearable sensors demonstrated significant deficits in PD-PN cases in the OFF medication state [14, 15, 16].
   • Gait speed was significantly slower (P value equal 0.005) [14, 15].
   • Stride length was significantly shorter (P value equal 0.029) [14, 15].
   • PN patients exhibited smaller toe-off angles (P-value equal 0.002) throughout straight walking [14, 15].
   • The effects on gait remained, albeit moderately reduced, in the ON state [14, 15].
   • Gait parameters, including stride length and speed, can effectively explain most MDS-UPDRS III score variations [14, 15, 16].
3. **Balance and postural stability:** Significant differences in balance were observed only during the most challenging static balance tasks, specifically stance with closed eyes on a foam surface in the OFF medication state [14, 4, 3]. PN impairs stepping as a postural control mechanism, with PN patients requiring more steps for stability [3]. This sensory compromise forces reliance on hip strategies to maintain balance [3, 1, 2].

DISCUSSION

This review confirmed that PN is highly prevalent (up to 55%) in PD [6, 7, 14]. The high pooled prevalence of SFN (56.9%) and fiber loss observed in drug-naïve patients suggest that PN may be an intrinsic component of PD pathology [11, 10].

The link between PN and levodopa exposure is widely accepted, mediated by high Hcy and methylmalonic acid (MMA) levels [9, 12, 13]. However, the finding that PN occurs in de novo PD and is associated with high Hcy levels suggests that a non-levodopa-related metabolic contribution exists from early stages [10, 11].

The identification of vitamin B12 deficiency as a strong and modifiable risk factor for falls (OR 2.667) provides a clear target for intervention [7].

Gait analyses further support the functional burden of PN. Meta-analytic evidence demonstrated that PD patients exhibit slower gait velocity and shorter step length compared to healthy controls [17].

Longitudinal studies revealed progressive deterioration in gait parameters—including stride length and variability—over a 6-year period in incident PD, even in the absence of neuropathy, underscoring the additive risk when PN is present [18]. Large-fiber neuropathy itself may independently impair motor performance and contribute to more severe gait disturbances, highlighting the need to screen for both small and large fiber involvement [19].

The functional impact of PN is independent and profound. PN acts as a genuine risk factor for falls [4, 5, 3]. The deficits—slower speed, shorter stride length, and reduced toe-off angles—are quantifiable using objective techniques like inertial measurement units (IMUs). The inability of the neuromuscular control system to respond to reduced peripheral sensory input forces PD-PN patients to adopt a cautious gait pattern [14, 15, 16, 20, 21].

The critical finding that PN patients demonstrate functional deficits and high fall rates without

significantly higher MDS-UPDRS motor scores confirms that PN introduces a distinct, non-dopaminergic source of axial instability that standard scales fail to capture [14, 4, 16]. This highlights the importance of comprehensive assessment methods, as advanced techniques (wearables & pose estimation) show high accuracy (up to 91%) in detecting early gait changes [15, 16, 20, 21].

CONCLUSION

Peripheral neuropathy is a highly prevalent (up to 55%) and significant comorbidity in Parkinson's disease. It functions as a genuine & independent risk factor for falls (OR 17.41) and mobility deficits. PN exacerbates gait impairment, resulting in quantifiable deficits like shorter stride length and slower gait speed. PN development is linked to long-term L-DOPA exposure and metabolic abnormalities, including low Vitamin B12 levels (OR 2.667). PN deficits are often independent of traditional PD motor severity. Routine evaluation and management of PN using neurophysiological assessment, including screening for underlying metabolic causes and applying PN-oriented physical therapy (e.g., balance and stepping strategies), are essential for reducing disability and improving the quality of life in Parkinson's disease cases.

DECLARATIONS

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