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Review Article

Peripheral neuropathy in idiopathic Parkinson's disease: A systematic review

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ABSTRACT

Background: Parkinson's disease (PD) has been associated with peripheral neuropathy (PN). PN has been demonstrated in some rare genetic forms of PD (e.g. PARK2 mutations) but has also been linked to levodopa exposure.
Objective: The aim of this systematic review is to clarify any evidence of peripheral nervous system involvement in idiopathic PD.
Methods: A systematic computer-based literature search was conducted on PubMed database.
Findings: The pooled estimate of the prevalence of large fiber PN in PD was 16.3% (based on 1376 patients). The pooled estimate of the prevalence of biopsy-proven small fiber neuropathy was 56.9% (based on 72 patients). Large fiber PN in PD is in the majority of cases distal, symmetrical, axonal and predominantly sensory. There are, however, few reports of chronic idiopathic demyelinating polyneuropathy and very occasional cases of acute neuropathies. Although nerve conduction studies have been performed in the majority of the studies, they included only a limited number of nerves, mainly in the lower limbs.
There is little evidence to support a direct link between levodopa treatment and the development of PN in idiopathic PD. In the majority of the cases PN has been linked to abnormalities in vitamin B12, methylmalonic acid or fasting homocysteine levels. Additional aetiological risk factors for PN may be responsible for any apparent link between PD and PN.
Conclusions: Large-scale prospective studies with long-term follow-up with detailed baseline assessments are needed in order to understand the natural history of PN in PD, both on clinical and neurophysiological parameters.

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1. Introduction

The term peripheral neuropathy (PN) refers to any disorder of the peripheral nervous system including single and multiple mononeuropathies (i.e. mononeuritis multiplex), symmetrical involvement of many nerves (polyneuropathy) or isolated involvement of sensory ganglia (ganglionopathies) [1]. Further classification depends on a mixture of phenomenological, neurophysiological, pathological and aetiological parameters [2]. There is sparse robust epidemiological data on polyneuropathies of any cause in the general population, the current estimates being between 2.4% and 8.0% [3–5]. Population-based studies have shown that prevalence of PN increases with age [5], being a common cause of chronic pain in the elderly [6].

An association between PN and Parkinson's disease (PD) has been described in some rare genetic forms of PD, such as in patients with PARK2 mutations [7] and has also been linked to levodopa exposure [8].

The aim of this work was systematically to review available studies on PN in idiopathic Parkinson's disease (IPD) in an attempt to clarify causal mechanisms of peripheral nervous system involvement in IPD.

2. Methods

2.1. Literature search strategy

A systematic computer-based literature search was conducted on April 9th, 2017 using the PubMed database. For the search we used two Medical Subject Headings (MeSH) terms in title or abstract. Term A was “Parkinson” or “Parkinson's” and Term B was “neuropathy” OR “polyneuropathy”. Limitations included human species, English language and full text available. We also perused the reference lists of the papers in order to find papers not identified through the search strategy.

2.2. Inclusion and exclusion criteria

To be included in the review, the articles had to meet the following criteria:

(1) to involve single cases or cases series with the combination of PN and IPD,
(2) to study human adult subjects.

Exclusion criteria included:

(1) book chapters, reviews, letters to the editor and editorials not providing new data.
(2) Papers referring only to autonomic neuropathy.

3. Results

3.1. Search results

This search strategy resulted in the identification of 278 articles. After the eligibility assessment, 243 articles were excluded and 35 met the inclusion criteria. Scanning the reference lists 3 more papers were identified. In total, 38 papers were used for this review. Table 1 summarizes the characteristics of these papers (full details for each study are available as an online Supplement). Fig. 1 illustrates the study selection process.

3.2. Epidemiology of large fiber neuropathy

Large fiber neuropathy occurs when the Aα and Aβ myelinated fibers are affected and is diagnosed via nerve conduction studies. The first report of patients with PD who developed PN was in 1991 (Bulling et al. [9]). The prevalence of large fiber neuropathy in IPD ranges from 6% to 58% [10–12]. The pooled estimate of the prevalence of large fiber neuropathy reported in 17 studies with a total of 1376 patients was 16.3%. This is higher than the prevalence of PN in the general population [3,4].

As shown in Table 1, the male: female ratio of patients with PD who developed PN is identical to the gender ratio of the patients with PD who did not develop PN. The mean age of patients who developed PN is higher compared to the mean of the studied populations (69.4 versus 66.0 years respectively).

3.3. Epidemiology of small fiber neuropathy

In small fiber neuropathy (SFN), the unmyelinated C and the thinly myelinated Ad fibers are affected. The clinical features (i.e. pinprick and thermal sensory loss, allodynia, hyperalgesia etc.), results of associated special investigations (i.e. quantitative sensory testing and altered intra-epidermal nerve fiber density) and normal nerve conduction studies are used to diagnose SFN [13]. Skin biopsy, as it is objective, appears to have greater diagnostic precision than the clinical examination and quantitative sensory testing in the diagnosis of small fiber neuropathy [14]. Kass-Iliyya et al. recently showed that corneal confocal

Table 1
Characteristics of papers included in the review. Full details for each study are available as an online Supplement.

Types of publications	
Case reports	4
Case series/open label studies	18
Case – controlled studies	16
Number of all PD patients studied	
Total number of PD patients	1651
Range	1–500
Mean number of patients per study (SD)	43.4 (94.5)
Median	20
Demographics of all PD patients studied[a]	
Male:Female	3:2
Mean age	66.1 years
Mean disease duration	7.9 years
Number of all PD patients with PN studied[b]	
Total number of PD patients	258
Range	1–49
Mean number of patients per study (SD)	7.6 (11.8)
Median	3
Demographics of all PD patients with PN studied[a]	
Male:Female	3:2
Mean age	69.4 years
Mean disease duration	8.6 years
Year of publication	
Range	1991 to 2016
Number of publications per decade	
Until 2000	1
2000–2009	6
2011–now	31

[a] Where data were provided.
[b] Large fiber PN confirmed electrophysiologically.