King's Research Portal

DOI:

[10.1016/j.jns.2017.05.023](https://doi.org/10.1016/j.jns.2017.05.023)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Zis, P., Grünewald, R. A., Ray Chaudhuri, K., & Hadjivassiliou, M. (2017). Peripheral neuropathy in idiopathic Parkinson's disease: A systematic review. *Journal of the Neurological Sciences*.
<https://doi.org/10.1016/j.jns.2017.05.023>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

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

Panagiotis Zis, Richard A. Grunewald, Ray Kallol Chaudhuri, Marios Hadjivassiliou

PII: S0022-510X(17)30319-2
DOI: doi: [10.1016/j.jns.2017.05.023](https://doi.org/10.1016/j.jns.2017.05.023)
Reference: JNS 15330

To appear in: *Journal of the Neurological Sciences*

Received date: 23 January 2017
Revised date: 9 May 2017
Accepted date: 10 May 2017

Please cite this article as: Panagiotis Zis, Richard A. Grunewald, Ray Kallol Chaudhuri, Marios Hadjivassiliou , Peripheral neuropathy in idiopathic Parkinson's disease: A systematic review. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Jns(2017), doi: [10.1016/j.jns.2017.05.023](https://doi.org/10.1016/j.jns.2017.05.023)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Peripheral neuropathy in Idiopathic Parkinson's disease: A systematic review.

Panagiotis Zis, PhD ^{1,2} – Corresponding author

Richard A. Grünewald, DPhil¹

Ray Kallol Chaudhuri, MD, ³

Marios Hadjivassiliou, MD ^{1,2}

1. Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
2. University of Sheffield, UK
3. National Parkinson Foundation International Centre of Excellence, King's College London and Kings College Hospital NHS Foundation Trust, London, UK

Corresponding author contact details

Academic Department of Neurosciences and University of Sheffield

Royal Hallamshire Hospital

Glossop Rd, Sheffield, South Yorkshire S10 2JF

takiszis@gmail.com

Tel. +44 114 271 1900

Author contributions

PZ and KRC have conceptualized the review. PZ carried out the systematic literature review and wrote the manuscript. RAG, KRC, and MH revised the manuscript.

Keywords: Polyneuropathy, idiopathic, Parkinson's disease

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 1,376 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.

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

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.

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*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). Figure 1 illustrates the study selection process.

Epidemiology of large fiber neuropathy

Large fiber neuropathy occurs when the A α and A β 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 1,376 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).

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 fibre 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-Illyya et al. recently showed that corneal confocal microscopy could be used as an alternative method to demonstrate non-invasively small nerve fiber damage in PD [15]. In this study it was shown that patients with PD have an increased corneal nerve fiber length and corneal nerve branching density, as well as a decreased corneal nerve fiber density. However, these results were exactly opposite to the ones reported in a study conducted by Podgorny et al. who showed that patients with early PD (drug naïve or recently started on treatment) had significantly reduced corneal nerve fiber densities and lengths compared to controls [16]. Although both studies included small number of patients, and therefore might be underpowered, the contradictory results could also possibly be explained by the fact that the study by Podgorny et al. mainly involved drug-naïve or early treated patients [16].

SFN in PD has been reported since 2008 when Novak et al. demonstrated reduced small fiber density in skin biopsies from patients with PD [17]. Nolano et al. performed quantitative sensory testing and skin biopsies in patients with PD and found a significant increase in tactile and thermal thresholds, a significant reduction in mechanical pain perception and a significant loss of epidermal nerve fibers (ENFs)

and Meissner corpuscles (MCs) in patients with PD compared to controls [18, 19]. Reported prevalence of SFN, as this was determined by the intra-epidermal nerve fiber density, ranges from 37% [20] to 91% [21]. The pooled estimate of the prevalence of small fiber neuropathy based on the skin biopsy as this has been reported in 3 studies of a total of 72 patients with PD is 56.9% [20 – 22]. Given the small number of participants in each study this figure should be interpreted with caution.

Neurophysiological types of chronic neuropathy in PD

Large fiber neuropathies can be broadly classified as axonal, where axons are affected most commonly in proportion to their length (length-dependent polyneuropathy) or demyelinating, affecting the myelin sheath around axons and impairing the ability of the axons to speedily conduct electrical impulses resulting in slow conduction or conduction block [1].

Neuropathy in PD is in the majority of cases distal, symmetrical, axonal and predominantly sensory. There are, however, few reports of chronic inflammatory demyelinating polyneuropathy (CIDP). In their study, Toth et al. reported that out of 49 patients with PD and PN, 94% had sensorimotor axonal neuropathy and 6% had CIDP [23]. In a case series reported by Gondim Fde et al., 1 out of 10 patients reported had CIDP [24]. A case of distal acquired demyelinating symmetric (DADS) neuropathy – which is considered a subtype of CIDP – has been recently reported by McGinty et al. [25] and has been linked with the anti-TNF- α therapy that the patient was receiving for his rheumatoid arthritis. Such reports of patients with PD with co-incident autoimmune diseases [26] suggest a possible role of the immune system in the pathogenesis of at least some cases of neuropathy in PD

Acute polyneuropathies

Isolated cases of patients with PD who developed acute polyneuropathies have been reported. The first such report was by Rajabally et al. [27] who described a patient

who developed acute motor axonal neuropathy (AMAN) following *Campylobacter jejuni* infection. Acute inflammatory demyelinating polyneuropathy (classical Guillain-Barre syndrome) with positive anti-ganglioside antibodies has been reported by Galazky et al. during intrajejunal levodopa infusion therapy [28].

Pathological findings - nerve biopsies

Sural nerve biopsies have been reported in 2 patients with PD who had developed sub-acute axonal neuropathy associated with cobalamin and vitamin B6 deficiency during intestinal levodopa therapy. The biopsies showed reduction in myelinated nerve fiber density and endoneurial oedema. Myelin debris was found in several endoneurial macrophages, indicating recent nerve fiber breakdown. Inflammatory infiltrates of CD8-immunoreactive T-cells were absent [29]. Evidence of inflammatory changes (perivascular lymphocytic cuffing) had been found in sural nerve biopsies in one of 3 patients reported by Kimber et al. [30] when mild inflammatory infiltration lymphocytes in one out of 2 patients reported by Cáceres-Redondo et al. [31]

Vital et al. conducted a pathological study of peripheral nerves from patients with PN and demonstrated intra-axonal ubiquitin aggregates were more numerous in the patients with PN and PD compared to patients without PD [32]. It is possible that the prevalence of ubiquitin aggregates in patients with PD is the consequence of the underlying neurodegenerative process [32].

Pathological findings – skin biopsies

Small fiber density is reduced in PD compared with healthy controls [15, 18 - 21] and patients with parkinsonism [17, 21] suggesting that skin biopsy may be also contribute to the differential diagnosis of IPD and parkinsonism [21].

Wang et al. studied the α -synuclein deposition in cutaneous sensory nerves and showed that is increased in cutaneous sympathetic adrenergic and sympathetic cholinergic fibers but not sensory fibers of patients with PD compared to controls [21]. Donadio et al. showed that neuritic α -synuclein inclusions are correlated with a small-fiber neuropathy suggesting a possible direct role of phosphorylated α -synuclein in peripheral nerve fiber damage [33].

Risk factors and role of levodopa

The term idiopathic neuropathy refers to those neuropathies where no aetiology can be identified despite extensive and appropriate investigations [1]. The reported prevalence of idiopathic neuropathies among patients with PD varies widely, and investigations about possible causes of polyneuropathy may have been incomplete in some reports [1]. Some studies included in this review have not stated whether extensive thorough investigations were done to identify potential risk factors [34, 35] or, in other studies, the authors have only checked for very common risk factors such as alcohol exposure, diabetes and hypovitaminosis [10, 32, 36, 37].

Toth et al. reported the largest case series of patients with PD and PN [23]. Out of 49 patients with PD and PN, 8 patients were found to have diabetes or impaired glucose tolerance, 4 patients monoclonal gammopathy of uncertain significance and 3 patients had CIDP. Idiopathic PN was identified in 34 patients with PD. However, 32 of these (94%) had abnormalities in vitamin B12, fasting methylmalonic acid (MMA) or fasting homocysteine concentrations (Hcy), leaving only 2 patients (4.1% of the case series) with truly idiopathic neuropathy. In this study, it was suggested that cumulative lifetime levodopa dosage and fasting MMA levels were associated with PN severity and concluded that PN in PD may either be associated with iatrogenic cobalamin metabolic abnormalities or be a peripheral nervous system manifestation of PD [23]. Increased Hcy and low B12 levels have been reported in smaller case series of patients with PD and PN [29 -31, 38 – 43].

Ceravolo et al. reported that the risk of neuropathy in PD is independently associated only to age and duration of exposure to levodopa and is not influenced by disease duration, disease severity, serum vitamin B12 or serum Hcy level [8].

Data on levodopa-naïve patients show that there is no difference between the epidermal nerve fiber density in treated and untreated patients, suggesting that epidermal nerve fiber density is unrelated to drug treatment [19]. In a study conducted by Shahrizaila et al. the electrodiagnostic criteria for distal symmetric polyneuropathy were fulfilled in 24% of treated patients and in 23% of untreated patients, demonstrating no difference in the prevalence of PN in patients with PD taking chronic levodopa therapy versus levodopa-naïve patients [10]. Rajabally et al. found that the prevalence of PN in levodopa-naïve patients with PD was significantly lower compared to levodopa treated (12.1% versus 36.1%) after a regression analysis they concluded that neuropathy was only independently associated with age and serum folate concentration [42].

Protective role of COMT

In a recent study Cossu et al compared 144 patients with PD who have been on levodopa for more than three years not receiving entacapone with 53 patients who have also been on levodopa for more than three years, but were also receiving entacapone [44]. The prevalence of neuropathy in the latter group (prevalence 5.7%) was significantly lower than the patients not receiving entacapone (prevalence 19.4%). This finding, suggests that the use of catechol-O-methyltransferase-inhibitors could have a protective effect on the development of PN.

Intestinal levodopa infusion studies

The first reports of PN during continuous intestinal infusion of levodopa suggested that patients might develop subacute PN secondary to hypovitaminosis, mainly B12

deficiency [29, 38, 39, 45], although isolated case reports described patients with subacute PN without cobalamin deficiency [46].

In a small case controlled study of intestinal levodopa infusion versus oral drugs, Jugel et al. reported that neurophysiological abnormalities were more severe in the group who had intestinal levodopa infusion [35]. Contrary to this finding, Mancini et al. in a large case controlled study compared the prevalence of PN in patients on intestinal levodopa infusion with patients on oral levodopa and with patients on other dopaminergic treatment, and found a higher prevalence of PN in patients treated with intestinal levodopa (28%) and oral levodopa treated patients (20%) compared to patients on other dopaminergic treatments (6%). No difference between the intestinal and oral levodopa groups was observed [37].

In a prospective study of assessment of PN during intestinal levodopa infusion, Merola et al. reported that intestinal levodopa infusion may worsen the neurophysiological and clinical features of pre-existing polyneuropathy, but these alterations are similar to those described during oral levodopa treatment [41]. The same group recently published their experience on 33 consecutive patients treated with intestinal levodopa infusion [47]. Of these, 10 patients (30.3%) had clinical or electrophysiological evidence of PN before the treatment with the intestinal levodopa infusion. Of the remaining 23 patients, almost half (47.8%) developed neuropathy during the intestinal levodopa infusion treatment; 2 developed subacute PN and 9 developed chronic PN (2 with clinical signs and 7 only with electrophysiological evidence).

Chang et al. suggested that clinicians should monitor for PN and for hypovitaminoses during intestinal levodopa infusion, as vitamin supplementation can reverse PN [40]. In a pilot prospective study assessing small nerve fiber impairment following intestinal levodopa infusion in 5 patients, Devigili et al showed that intestinal levodopa infusion could cause severe skin denervation and increased thermal thresholds [48]. Epidermal denervation occurred soon after starting treatment; axonal swellings and intraepidermal nerve fiber density reduction were detected

after 3 months, while almost complete denervation of the epidermis and dermal bundles appeared at 6 months [48].

Conclusion

The pooled estimate of the prevalence of large fiber neuropathy in idiopathic PD is estimated to be 16.3%. This is significantly higher compared to the prevalence of PN in the general population. However, this figure should be interpreted with caution, given the heterogeneity of the study populations and the fact that in some studies patients with risk factors such as diabetes and excessive alcohol consumption were excluded. Therefore, the prevalence of PN in PD might be even greater. In addition, the extent of investigations looking at other causes of PN in these patients was variable and often limited.

The role of levodopa on the development of PN is unclear. One study, showed that levodopa is independently associated to PN [42], however the number of patients in that study was too small securely to conclude that levodopa directly is responsible for the development of PN in PD. Available data on levodopa-naïve patients – which are especially important when describing populations of patients with PD [49 – 51] – have not shown difference in the prevalence of PN compared to levodopa treated patients. On the other hand the majority of studies showed that in most PD cases PN is associated with abnormalities in vitamin B12, MMA or and Hcy levels. Such abnormalities can occur as a result of malabsorption and it has been hypothesised that levodopa treatment might affect the vitamin absorption [52].

Although the number of studies of PN in PD is increasing, the number of patients with PD and PN reported in each is small. The largest study to date has included 49 patients with the combination of PD and PN [23]. 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.

Diagnosing PN based on symptom prevalence assessed by checklists and questionnaire has a risk of overestimating the prevalence of PN. This is exaggerated by the fact that patients with PD may experience sensory symptoms, i.e. neuropathic pain of central origin [53] rather than symptoms secondary to PN. PN can only be confirmed by neurophysiological assessment. In most studies included in this review nerve conduction studies (NCS) have been performed and data have been provided, however the NCS included only a limited number of nerves, mainly in the lower limbs. The differences in the techniques, the incomplete NCS and the lack of normative age-corrected data may influence the apparent prevalence of PN in PD. Although many centers have different ways to determine neurophysiologically the presence of neuropathy, sensory conduction studies of sural and radial nerves are recommended for the diagnosis of a mild axonal predominantly sensory neuropathy [54]. This should be complemented with at least one motor study, commonly of the tibial nerve [55], to confirm motor involvement. Early SFN assessment, involving quantitative sensory testing and corneal confocal microscopy may be a useful approach to the diagnosis of PN as it is known that at least some patients evolve from a strict SFN to large fiber PN [56, 57].

Disclosures: Nothing to disclose

Conflict of interest: None

References

1. Zis P, Sarrigiannis PG, Rao DG, Hewamadduma C, Hadjivassiliou M. Chronic idiopathic axonal polyneuropathy: a systematic review. *J Neurol*. 2016 Oct;263(10):1903-10.
2. Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. *Journal of neurology, neurosurgery, and psychiatry* 1997;62:310-318.
3. Bharucha NE, Bharucha AE, Bharucha EP. Prevalence of peripheral neuropathy in the Parsi community of Bombay. *Neurology* 1991;41:1315-1317.
4. Italian General Practitioner Study Group (IGPSG). Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions. I. Prevalence and general characteristics of the sample. *Neurology* 1995;45:1832-1836.
5. Hanewinkel R, Drenthen J, van Oijen M, Hofman A, van Doorn PA, Ikram MA. Prevalence of polyneuropathy in the general middle-aged and elderly population. *Neurology*. 2016 Nov 1;87(18):1892-1898.
6. Zis P, Daskalaki A, Boudouni I, Sykioti P, Varrassi G, Paladini A. Depression and chronic pain in the elderly: links and management challenges. *Clinical Interventions in Aging*, in press
7. Ohsawa Y, Kurokawa K, Sonoo M, Yamada H, Hemmi S, Iwatsuki K, Hagiwara H, Murakami T, Shirabe T, Shimizu T, Sunada Y. Reduced amplitude of the sural nerve sensory action potential in PARK2 patients. *Neurology*. 2005 Aug 9;65(3):459-62.
8. Ceravolo R, Cossu G, Bandettini di Poggio M, Santoro L, Barone P, Zibetti M, Frosini D, Nicoletti V, Manganelli F, Iodice R, Picillo M, Merola A, Lopiano L, Paribello A, Manca D, Melis M, Marchese R, Borelli P, Mereu A, Contu P, Abbruzzese G, Bonuccelli U. Neuropathy and levodopa in Parkinson's disease: evidence from a multicenter study. *Mov Disord*. 2013 Sep;28(10):1391-7.

9. Bulling MT, Wing LM, Burns RJ. Controlled release levodopa/carbidopa (Sinemet CR4) in Parkinson's disease--an open evaluation of efficacy and safety. *Aust N Z J Med*. 1991 Aug;21(4):397-400.
10. Shahrizaila N, Mahamad UA, Yap AC, Choo YM, Marras C, Lim SY. Is chronic levodopa therapy associated with distal symmetric polyneuropathy in Parkinson's disease? *Parkinsonism Relat Disord*. 2013 Mar;19(3):391-3.
11. Toth C, Breithaupt K, Ge S, Duan Y, Terris JM, Thiessen A, Wiebe S, Zochodne DW, Suchowersky O. Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease. *Ann Neurol*. 2010 Jul;68(1):28-36
12. de Araújo DF, de Melo Neto AP, Oliveira ÍS, Brito BS, de Araújo IT, Barros IS, Lima JW, Horta WG, Gondim Fde A. Small (autonomic) and large fiber neuropathy in Parkinson disease and parkinsonism. *BMC Neurol*. 2016 Aug 17;16:139.
13. Themistocleous AC, Ramirez JD, Serra J, Bennett DL. The clinical approach to small fibre neuropathy and painful channelopathy. *Pract Neurol*. 2014 Dec;14(6):368-79.
14. Hlubocky A, Wellik K, Ross MA, Smith BE, Hoffman-Snyder C, Demaerschalk BM, Wingerchuk DM. Skin biopsy for diagnosis of small fiber neuropathy: a critically appraised topic. *Neurologist*. 2010 Jan;16(1):61-3.
15. Kass-Iliyya L, Javed S, Gosal D, Kobylecki C, Marshall A, Petropoulos IN, Ponirakis G, Tavakoli M, Ferdousi M, Chaudhuri KR, Jeziorska M, Malik RA, Silverdale MA. Small fiber neuropathy in Parkinson's disease: A clinical, pathological and corneal confocal microscopy study. *Parkinsonism Relat Disord*. 2015 Dec;21(12):1454-60.
16. Podgorny PJ, Suchowersky O, Romanchuk KG, Feasby TE. Evidence for small fiber neuropathy in early Parkinson's disease. *Parkinsonism Relat Disord*. 2016 Jul;28:94-9.

17. Novak P, Marya NB, Whren K, Bhawan J. Dermal sheet preparations in the evaluation of dermal innervation in Parkinson's disease and multiple system atrophy. *J Cutan Pathol*. 2009 Mar;36(3):296-301.
18. Nolano M, Provitera V, Estraneo A, Selim MM, Caporaso G, Stancanelli A, Saltalamacchia AM, Lanzillo B, Santoro L. Sensory deficit in Parkinson's disease: evidence of a cutaneous denervation. *Brain*. 2008 Jul;131(Pt 7):1903-11.
19. Nolano M, Provitera V, Lanzillo B, Santoro L. Neuropathy in idiopathic Parkinson disease: an iatrogenic problem? *Ann Neurol*. 2011 Feb;69(2):427-8.
20. Doppler K, Ebert S, Uçeyler N, Trenkwalder C, Ebentheuer J, Volkmann J, Sommer C. Cutaneous neuropathy in Parkinson's disease: a window into brain pathology. *Acta Neuropathol*. 2014 Jul;128(1):99-109.
21. Giannoccaro MP, Donadio V, Incensi A, Pizza F, Cason E, Di Stasi V, Martinelli P, Scaglione C, Capellari S, Treglia G, Liguori R. Skin biopsy and I-123 MIBG scintigraphy findings in idiopathic Parkinson's disease and parkinsonism: a comparative study. *Mov Disord*. 2015 Jun;30(7):986-9.
22. Wang N, Gibbons CH, Lafo J, Freeman R. α -Synuclein in cutaneous autonomic nerves. *Neurology*. 2013 Oct 29;81(18):1604-10.
23. Toth C, Brown MS, Furtado S, Suchowersky O, Zochodne D. Neuropathy as a potential complication of levodopa use in Parkinson's disease. *Mov Disord*. 2008 Oct 15;23(13):1850-9.
24. Gondim Fde A, de Oliveira GR, Peixoto AA Jr, Horta WG. A case series of peripheral neuropathy in patients with Parkinson's disease. *Ann Neurol*. 2010 Dec;68(6):973-5.
25. McGinty RN, McNamara B, Moore H. DADS neuropathy associated with anti-TNF- α therapy. *BMJ Case Rep*. 2015 Nov 25;2015. pii: bcr2015211781.
26. Zis P, Argiriadou V, Temperikidis PP, Zikou L, Tzartos SJ, Tavernarakis A. Parkinson's disease associated with myasthenia gravis and rheumatoid arthritis. *Neurol Sci*. 2014 May;35(5):797-9.

27. Rajabally YA, Ramlackhansingh A, Fraser M, Abbott RJ. Neuroleptic malignant syndrome and acute motor axonal neuropathy after *Campylobacter jejuni* infection. *Neurophysiol Clin*. 2009 Aug;39(3):135-8.
28. Galazky I, Schoof J, Stallforth S, Kupsch A, Heinze HJ, Kluge C. Guillain-Barre/CIDP-like neuropathy in two parkinsonian patients following intestinal levodopa/carbidopa treatment. *Parkinsonism Relat Disord*. 2014 Jan;20(1):125-7.
29. Urban PP, Wellach I, Faiss S, Layer P, Rosenkranz T, Knop K, Weis J. Subacute axonal neuropathy in Parkinson's disease with cobalamin and vitamin B6 deficiency under duodopa therapy. *Mov Disord*. 2010 Aug 15;25(11):1748-52.
30. Kimber T, Blumbergs P, Thompson P. Severe ataxic polyneuropathy associated with chronic levodopa use in Parkinson's disease. *Parkinsonism Relat Disord*. 2013 Sep;19(9):847-9.
31. Cáceres-Redondo MT, Carrillo F, Lama MJ, Huertas-Fernández I, Vargas-González L, Carballo M, Mir P. Long-term levodopa/carbidopa intestinal gel in advanced Parkinson's disease. *J Neurol*. 2014 Mar;261(3):561-9.
32. Vital A, Meissner WG, Carron MH, Martin-Negrier ML, Bezard E, Tison F, Vital C. Intra-axonal protein aggregation in the peripheral nervous system. *J Peripher Nerv Syst*. 2014 Mar;19(1):44-9.
33. Donadio V, Incensi A, Leta V, Giannoccaro MP, Scaglione C, Martinelli P, Capellari S, Avoni P, Baruzzi A, Liguori R. Skin nerve α -synuclein deposits: a biomarker for idiopathic Parkinson disease. *Neurology*. 2014 Apr 15;82(15):1362-9.
34. Chovancova Z, Kanovsky P, Dufek J, Nevrlý M, Otruba P. Peripheral nerve involvement and severity of motor disorder in Parkinson's disease: a correlational study. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2009 Mar;153(1):59-62.
35. Jügel C, Ehlen F, Taskin B, Marzinzik F, Müller T, Klostermann F. Neuropathy in Parkinson's disease patients with intestinal levodopa infusion versus oral drugs. *PLoS One*. 2013 Jun 20;8(6):e66639.

36. Rajabally YA, Martey J. Neuropathy in Parkinson disease: prevalence and determinants. *Neurology*. 2011 Nov 29;77(22):1947-50
37. Mancini F, Comi C, Oggioni GD, Pacchetti C, Calandrella D, Coletti Moja M, Riboldazzi G, Tunesi S, Dal Fante M, Manfredi L, Lacerenza M, Cantello R, Antonini A. Prevalence and features of peripheral neuropathy in Parkinson's disease patients under different therapeutic regimens. *Parkinsonism Relat Disord*. 2014 Jan;20(1):27-31.
38. Manca D, Cossu G, Murgia D, Molari A, Ferrigno P, Marcia E, Melis M. Reversible encephalopathy and axonal neuropathy in Parkinson's disease during duodopa therapy. *Mov Disord*. 2009 Nov 15;24(15):2293-4.
39. Santos-García D, de la Fuente-Fernández R, Valldeoriola F, Palasí A, Carrillo F, Grande M, Mir P, De Fabregues O, Casanova J. Polyneuropathy while on duodenal levodopa infusion in Parkinson's disease patients: we must be alert. *J Neurol*. 2012 Aug;259(8):1668-72.
40. Chang FC, Kwan V, van der Poorten D, Mahant N, Wolfe N, Ha AD, Griffith JM, Tsui D, Kim SD, Fung VS. Intraduodenal levodopa-carbidopa intestinal gel infusion improves both motor performance and quality of life in advanced Parkinson's disease. *J Clin Neurosci*. 2016 Mar;25:41-5.
41. Merola A, Zibetti M, Rizzone MG, Troiano M, Artusi CA, Angrisano S, Cocito D, Lopiano L. Prospective assessment of peripheral neuropathy in Duodopa-treated parkinsonian patients. *Acta Neurol Scand*. 2014 Jan;129(1):e1-5.
42. Rajabally YA, Martey J. Levodopa, vitamins, ageing and the neuropathy of Parkinson's disease. *J Neurol*. 2013 Nov;260(11):2844-8.
43. Meppelink AM, Nyman R, van Laar T, Drent M, Prins T, Leenders KL. Transcutaneous port for continuous duodenal levodopa/carbidopa administration in Parkinson's disease. *Mov Disord*. 2011 Feb 1;26(2):331-4.
44. Cossu G, Ceravolo R, Zibetti M, Arca R, Ricchi V, Paribello A, Murgia D, Merola A, Romagnolo A, Nicoletti V, Palermo G, Mereu A, Lopiano L, Melis M, Abbruzzese G, Bonuccelli U. Levodopa and neuropathy risk in

- patients with Parkinson disease: Effect of COMT inhibition Parkinsonism Relat Disord. 2016 Jun;27:81-4.
45. Klostermann F, Jugel C, Müller T, Marzinzik F. Malnutritional neuropathy under intestinal levodopa infusion. J Neural Transm (Vienna). 2012 Mar;119(3):369-72.
46. Lehnerer SM, Fietzek UM, Messner M, Ceballos-Baumann AO. Subacute peripheral neuropathy under duodopa therapy without cobalamin deficiency and despite supplementation. J Neural Transm (Vienna). 2014 Oct;121(10):1269-72.
47. Merola A, Romagnolo A, Zibetti M, Bernardini A, Cocito D, Lopiano L. Peripheral neuropathy associated with levodopa-carbidopa intestinal infusion: a long-term prospective assessment. Eur J Neurol. 2016 Mar;23(3):501-9
48. Devigili G, Rinaldo S, Lettieri C, Eleopra R. Levodopa/carbidopa intestinal gel therapy for advanced Parkinson Disease: AN early toxic effect for small nerve fibers? Muscle Nerve. 2016 Nov;54(5):970-972.
49. Zis P, Rizos A, Martinez-Martin P, Pal S, Silverdale M, Sharma JC, Sauerbier A, Chaudhuri KR. Non-motor symptoms profile and burden in drug naïve versus long-term Parkinson's disease patients. J Parkinsons Dis. 2014;4(3):541-7.
50. Zis P, Martinez-Martin P, Sauerbier A, Rizos A, Sharma JC, Worth PF, Sophia R, Silverdale M, Chaudhuri KR. Non-motor symptoms burden in treated and untreated early Parkinson's disease patients: argument for non-motor subtypes. Eur J Neurol. 2015 Aug;22(8):1145-50.
51. Zis P, Erro R, Walton CC, Sauerbier A, Chaudhuri KR. The range and nature of non-motor symptoms in drug-naïve Parkinson's disease patients: a state-of-the-art systematic review. npj Parkinson's Disease. 2015 Jul 9;1:15013.
52. Lökk J. Treatment with levodopa can affect latent vitamin B 12 and folic acid deficiency. Patients with Parkinson disease run the risk of elevated homocysteine levels. Lakartidningen. 2003 Aug;100(35):2674-7.

53. Zis P, Sokolov E, Chaudhuri KR. An overview of pain in Parkinson's. An Introduction to Pain and Its Relation to Nervous System Disorders. 2016 May 2:387.
54. Rutkove SB, Kothari MJ, Raynor EM, Levy ML, Fadic R, Nardin RA. Sural/radial amplitude ratio in the diagnosis of mild axonal polyneuropathy. Muscle Nerve. 1997 Oct;20(10):1236-41.
55. Buschbacher RM. Tibial nerve motor conduction to the abductor hallucis. Am J Phys Med Rehabil. 1999 Nov-Dec;78(6 Suppl):S15-20.
56. Periquet MI, Novak V, Collins MP, Nagaraja HN, Erdem S, Nash SM, Freimer ML, Sahenk Z, Kissel JT, Mendell JR. Painful sensory neuropathy: prospective evaluation using skin biopsy. Neurology. 1999 Nov 10;53(8):1641-7.
57. Hoitsma E, Reulen JP, de Baets M, Drent M, Spaans F, Faber CG. Small fiber neuropathy: a common and important clinical disorder. J Neurol Sci. 2004 Dec 15;227(1):119-30.

Figure 1

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	1,651
Range	1 – 500
Mean number of patients per study (SD)	43.4 (94.5)
Median	20
Demographics of all PD patients studied*	
Male : Female	3:2
Mean age	66.1 years
Mean disease duration	7.9 years
Number of all PD patients with PN studied**	
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*	
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

*where data were provided

**large fiber PN confirmed electrophysiologically

ACCEPTED MANUSCRIPT

Highlights

- The prevalence of large fiber neuropathy in idiopathic PD is estimated to be 16%
- The role of levodopa on the development of PN is still unclear
- Large studies with neurophysiologically confirmed neuropathy in PD are needed