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Editor's comment: The possible relationship between Parkinson's disease (PD) and peripheral neuropathy has received increasing attention and scrutiny in recent years and with the plethora of publications on the topic, confusion has multiplied. If peripheral neuropathy indeed is more common in PD, whether it is part of the disease process itself or a complication of PD therapy, specifically of levodopa administration, also has been the subject of controversy. Comi and colleagues provide us with a thorough, perceptive, and very welcome review of these issues. They also posit that in PD peripheral neuropathy may have two faces: a small fiber neuropathy may be intrinsic to PD itself, whereas medium-large fiber neuropathy may represent a complication of levodopa therapy in individuals with advanced PD, particularly in persons receiving levodopa-carbidopa intestinal infusion. Although there are as yet no definitive answers, awareness of these issues is important for neurologists and this review provides a very nice foundation for this.

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Review

Peripheral nervous system involvement in Parkinson's disease: Evidence and controversies

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ABSTRACT

Background: In recent years, non-motor features of Parkinson's disease (PD) have received increasing attention and PD is currently considered a systemic rather than a pure basal ganglia disorder. Among the systemic features, peripheral neuropathy (PN) is a recent acquisition since the first case–control study reporting increased frequency of PN in PD dates back to 2008.
Methods: We reviewed available literature on peripheral nervous system (PNS) involvement in PD.
Results: Evidence of α-synuclein deposition in the PNS and small nerve fiber deterioration in both drug-naïve and treated PD patients is becoming stronger. In addition, several recent reports documented a significant role of levodopa exposure together with group B vitamin deficiency in facilitating the development of PN and case reports suggested that treatment with continuous levodopa intestinal infusion may increase the risk of acute PN compared to both oral levodopa and other dopaminergic treatments.
Conclusion: It is currently debated whether PN is an intrinsic disease-related feature, a consequence of levodopa treatment or both. In this review, we will discuss the different hypotheses, as well as our perspective on open issues and controversies.

1. Introduction

1.1. Parkinson's disease: a systemic disease

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder, and is clinically defined by the presence of resting tremor, rigidity and bradykinesia [1]. These features are collectively referred to as motor symptoms and mostly correlated to loss of dopaminergic neurons in the *pars compacta* of midbrain *substantia nigra*. The histological hallmark of the disease is the presence in the surviving neurons of intracytoplasmic inclusions known as Lewy bodies, mainly composed by α-synuclein aggregates. α-synuclein exerts multiple functions in health and disease, and its role in PD is not fully defined yet. It is believed that the accumulation of this protein may exert a detrimental effect on survived neurons, partly due to the activation of pro-inflammatory

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microglial cells [2,3]. Furthermore, evidence suggests that α-synuclein deposits may impair axonal transport [4].

The traditional view of PD as a basal ganglia disorder is counterbalanced by strong clinical and neuropathological evidence of systemic involvement. Indeed, PD patients present a wide range of non-motor features, including anosmia, sleep disturbances, constipation, mood deflection and pain, and their onset can even precede motor impairment [5]. Lewy bodies are not exclusively present in the basal ganglia, but can be detected, sometimes before clinical diagnosis, in several other nervous structures such as the olfactory cortex, brainstem nuclei, and enteric, pelvic and cardiac ganglia [6]. Furthermore, α-synuclein was shown to be highly expressed in the skin of PD patients, namely in the spinous cell layer, pilosebaceous unit, and eccrine glands, whereas it is scarcely expressed in atypical PD, and absent in controls [7].

Since the peripheral nervous system (PNS) is a target of α-synuclein deposition, there is growing interest in assessing whether the intrinsic pathogenetic features of PD may predispose to peripheral neuropathy (PN). In fact, several recent reports have documented increased frequency of PN in PD patients compared to age-matched healthy subjects. Most studies included patients undergoing pharmacological treatment and correlations with levodopa (LD) exposure and alterations in vitamin B12 (VB12) metabolism were found in independent reports, thus rising the question on whether PN is an additional systemic feature of PD, or a side effect of pharmacological treatment.

In the following sections we will review the evidence in both directions, and discuss which controversies are still to be unraveled.

2. Parkinson's disease is a determinant of neuropathy

Evidence of pathological changes in the PNS of PD patients is rapidly accumulating. α-synuclein aggregates have been detected in the pharyngeal motor and sensory branch of vagus nerve, in the glossopharyngeal nerve and in the internal superior laryngeal nerve in PD patients with dysphagia [8,9]. Lewy bodies have also been found in the dorsal vagus ganglion and parasympathetic sacral nuclei, as well as in the enteric nervous system, and cardiac and pelvic plexus, even in early disease stages [10–14]. Furthermore, experimental evidence from animal models suggests that α-synuclein may be involved in axonal degeneration following traumatic peripheral nerve injury [15]. Both cutaneous fibers abnormalities and α-synuclein deposition have been detected. One report showed that PD patients display loss of epidermal nerve fibers and Meissner corpuscles, clinically correlated to sensory dysfunction [16] (Table 1). Moreover, presence of α-synuclein aggregates in unmyelinated fibers of the dermis, and distal sensory and autonomic neuropathy have been reported in PD as well as other Lewy body diseases [17] (Table 1). Notably, α-synuclein deposition was detected in pilomotor and sudomotor but not in sensory nerves [18–20] (Table 1). Intriguingly, cutaneous abnormalities may be detected also in recently diagnosed/untreated PD patients and α-synuclein ratio, i.e. α-synuclein deposition normalized to nerve fiber density, positively correlates with Hohen & Yahr stage, suggesting that PNS involvement is a primary expression of PD instead of a consequence of its treatment and that it evolves with disease progression [20] (Table 1). Accordingly, Donadio et al. recently detected phosphorylated α-synuclein deposition and small nerve fiber neuropathy in PD patients. Both findings were not present in healthy controls and in patients with other parkinsonian syndromes such as vascular parkinsonism, tauopathies and Parkin mutation carriers. Furthermore, no differences in disease duration, LD exposure and risk factors for neuropathy, including VB12 deficiency, were found in idiopathic PD compared to other parkinsonian syndromes [21] (Table 1). Similar results were recently reported by Doppler et al. who detected a significant difference in both phosphorylated α-synuclein deposition and loss of small nerve fibers between idiopathic PD patients and controls. Also, in this study the authors did not find a correlation between pathological findings and both cumulative LD intake and markers of LD toxicity and suggested that phosphorylated α-synuclein dermal deposition may be a diagnostic marker of PD, even though with a relatively low sensitivity [22] (Table 1). Phosphorylated α-synuclein deposition seems more typical of small nerve fibers. Indeed, a recent neuropathological study on superficial peroneal nerve biopsies in patients with axonal neuropathy identified increased frequency of intra-axonal ubiquitin and 14-3-3 β but not of

Table 1
Studies investigating intrinsic PNS damage in PD.

Authors	Study population	Number and percentage of reported cases	Main findings
Nolano et al. (2008) [16]	48 subjects (18 PD, 30 controls)	18/18 (100%) of PD patients, 0/30 (0%) of controls	Significant reduction of ENF and MC in PD. Normal ENG findings.
Ikemura et al. (2008) [19]	279 patients (85 PD, 194 patients without CNS LB pathology)	20/85 (24%) of PD patients, 0/194 (0%) of patients without CNS LB.	Anti-phosphorylated alpha-synuclein immunoreactivity in skin from the abdominal wall and upper arm.
Miki et al. (2010) [17]	20 PD patients, no control group	2/20 (10%) of PD patients.	Anti-phosphorylated alpha-synuclein immunoreactivity in the skin form chest wall and leg.
Nolano et al. (2011) [18]	3 PD patients, and re-assessment of the previous study population. No new control subjects	3/3 (100%) of PD patients.	Loss of ENF in both treated and untreated patients. Loss of MC only in treated patients
Wang et al. (2013) [20]	34 subjects (20 PD, 14 controls)	20/20 (100%) of PD patients, 0/14 (0%) of controls	Significant loss of IE and PM fibers, and morphologic changes to SM fibers in PD compared to controls. Greater α-synuclein deposition and higher α-synuclein ratios in PD compared to controls within PM and SM nerves
Donadio et al. (2014) [21]	71 subjects (21 PD, treated and untreated, 20 patients with other parkinsonian syndromes, 30 controls).	21/21 (100%) of PD patients, 0/50 (0%) of patients with other parkinsonian syndromes and controls	Anti-phosphorylated alpha-synuclein immunoreactivity in the skin form proximal and distal sites.
Doppler et al. (2014) [22]	66 subjects (31 PD, 35 controls)	16/31 (52%) of PD patients, 0/35 (0%) of controls	Anti-phosphorylated alpha-synuclein immunoreactivity in the skin from proximal and distal leg, back and index finger.

Abbreviations: CNS = central nervous system; ENF = epidermal nerve fibers; ENG = electroneurography; IE = intraepidermal; LB = Lewy bodies; MC = Meissner corpuscles; PD = Parkinson's disease; PM = pilomotor; SM = sudomotor.

Table 2
Studies investigating extrinsic determinants of PN in PD.

Authors	Study population	Number and percentage of reported cases	Main findings
ORAL LEVODOPA			
Müller et al. (2004) [30]	58 subjects (31 PD and 27 controls)	20/31 (64%) of PD patients, 0/27 of controls	Axonal sensory PN in PD patients. Correlation with high levels of Hcy
Toth et al. (2008) [27]	758 subjects (550 PD and 258 non-PD PN patients)	49/500 (9.8%) of PD patients, 34 of whom (6.4%) had idiopathic PN	Axonal PN. 3 patients had a CIDP-like pattern. 32/34 patients had elevated Hcy and MMA levels and decreased folate and VB12 levels
Toth et al. (2010) [26]	116 patients (58 PD patients and 58 controls)	32/58 (55%) of PD patients, 5/58 (9%) of controls.	Axonal predominantly sensory PN. Higher levels of MMA and Hcy in PD patients compared to controls
Gondim et al. (2010) [44]	10 PD patients, no control group	10/10 (100%) of PD patients.	Axonal sensory-motor PN
Rajabally et al. (2011) [28]	74 subjects (37 PD patients and 37 controls)	14/37 (37.8%) of PD patients, 3/37 (8.1%) of controls	Axonal PN. Correlation with VB12 deficiency
Kimber et al. (2013) [45]	4 PD patients, no control group	4/4 (100%) of PD patients.	Primary axonal pattern with secondary demyelination
Ceravolo et al. (2013) [25]	467 subjects (330 PD patients: 144 LELD, 103 SELD,83 NOLD and 137 controls)	28/144 (19.40%) of LELD PD, 7/103 (6.80%) of SELD PD; 4/83 (4.82%) of NOLD PD patients and 12/137 (8.76%) of controls	Axonal predominantly sensory PN. Age and duration of exposure to LD are best predictors of PN. Lower VB12, higher Hcy and LD dose in PD with PN versus non PN subjects
CONTINUOUS LEVODOPA INTESTINAL INFUSION			
Antonini et al. (2007) [49]	9 PD patients, no control group	9/9 (100%) of PD patients.	Acute or subacute axonal PN
Manca et al. (2009) [50]	Single case report, no control group	1/1 (100%) of PD patients.	Acute axonal PN
Urban et al. (2010) [42]	2 PD patients, no control group	2/2 (100%) of PD patients	Mild axonal sensory-motor PN
Santos-Garcìa et al. (2011) [43]	5 PD patients, no control group	1/5 (20%) of PD patients.	Subacute generalized axonal sensory-motor PN
Meppelink et al. (2011) [51]	15 PD patients, no control group	2/15 (13%) of PD patients.	Axonal sensory PN
Klostermann et al. (2012) [53]	2 PD patients, no control group	2/2 (100%) of PD patients.	Subacute axonal PN
Galazky et al. (2013) [46]	2 PD patients, no control group	2/2 (100%) of PD patients.	Mixed axonal- demyelinating PN after 4 and 13 months of CLDII, with CSF albumin-cytologic dissociation
Jugel et al. (2013) [48]	30 PD patients (15 on O-LD and 15 on CLDII)	15/15 (%) of O-LD patients, 15/15 (%) of CLDII patients	Axonal PN in both groups, with a more severe presentation in CLDII patients
Merola et al. (2014) [43]	15 PD patients, 10 with follow-up, no control group	3/15 (20%) of PD patients at baseline. After 9 months follow-up 1/10 (10%) of patients developed PN, 3/10 (30%) of patients had a worsening of pre-existing PN	Subacute sensory-motor axonal neuropathy
Mancini et al. (2014) [35]	150 PD patients (50 on ODT 50 on O-LD 50 on CLDII), no control group	3/50 (6%) of ODT, 10/50 (20%) of O-LD, 14/50 (28%) of CLDII patients	Axonal PN in % cases; acute (GBS-like) PN in % of CLDII

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; CLDII = continuous levodopa intestinal infusion; CSF = cerebrospinal fluid; GBS = Guillain-Barré syndrome; Hcy = Homocysteine; LELD = long exposure to levodopa; MMA = Methylmalonic acid; NOLD = no exposure to levodopa; O-LD = oral levodopa; ODT = other dopaminergic therapy; PD = Parkinson's disease; PN = Peripheral neuropathy; SELD = short exposure to levodopa; VB12 = vitamin B12.

phosphorylated α-synuclein aggregates in neuropathic PD patients compared to other patients with axonal neuropathy [23].

Finally, Vitale et al. detected peripheral sensorineural hearing loss in PD patients compared to matched healthy controls. Since no causal relationship with LD therapy was found, authors suggested that such sensory impairment may be an intrinsic PD feature [24].

3. Levodopa exposure is a determinant of neuropathy

Studies investigating the frequency of PN in PD patients on LD therapy, detected a significant increase compared to age-matched healthy subjects, although the reported data range varied from 4.8% [25] to 55% [26] (Table 2). This wide discrepancy is probably due to intrinsic differences of the study population in terms of age, disease duration and therapeutic regimen, as well as of the methodology used to detect PN: i) clinical signs only versus neurophysiological data, ii) diagnostic criteria used for diagnosis. Nonetheless, a correlation between PN development and both total LD dose and exposure to LD over time was observed [25–28].

Regarding the possible pathogenetic link between LD and PN, it has been suggested that LD could favor nerve damage by interacting with the homocysteine (hcy)/VB12 cycle.

Conversion of LD to dopamine requires a methyl group donation that is provided by adenosylmethionine, and such reaction leads to hcy formation. Subsequent hcy re-methylation requires VB12 as co-factor, and alternative ways of degradation require methylentetrahydrofolate and piridoxine (vitamin B6). Therefore, chronic LD use leads to methyl-group depletion and hcy overproduction. The final result is that chronic LD intake leads to hcy accumulation and vitamin B6, VB12 and folate depletion. Interestingly, inhibition of catechol-O-methyltransferase (COMT), which is an effective pharmacological approach to prolong LD effect in advanced PD patients, was shown to decrease hcy levels in LD treated PD patients [29].

PN may be part of a more complex clinical picture related to VB12 deficiency and a concurrent contribution to PNS damage by hyperhomocysteinemia has also been suggested [30–34]. Hyperhomocysteinemia is common in PD, and hcy level generally correlates with total LD dose [35,36] even if a genetic contribution from MTHRF polymorphism has also been reported [37–39]. In this context, COMT inhibition may theoretically protect the PNS from toxic damage. Nonetheless, no evidence supporting such approach to prevention/treatment of PN in PD was provided so far.

Lower VB12 blood levels in patients with PD and PN compared to patients with PD only and in high dose versus low dose treatment groups have been consistently reported [35]. Furthermore, LD daily dose and VB12 levels were shown to be inversely correlated [35].

Although marked VB12 deficiency in PD is uncommon, clinical improvement after VB12 supplementation was also reported in

symptomatic patients showing "borderline" VB12 values, suggesting that these patients should be treated, and that more sensitive indirect methods such as methilmalonic acid (MMA) measurement should be used [26].

On the other hand, vitamin deficiency cannot explain all reported cases of PN: some PN patients had normal VB12 blood values and a prospective study revealed both a new case of subacute PN and worsening of pre-existing PN in absence of any VB12, Hcy or MMA change [25]. Accordingly, Lehnerer et al. reported one case of severe subacute PN developing during continuous LD intestinal infusion (CLDII). Since such complication occurred despite normal VB12 and holotranscobalamin serum levels, authors suggested that PNS damage might be ascribed to accumulation of neurotoxic metabolites (e.g., MMA and Hcy) [40] (Table 2).

Although VB12 administration may provide benefit in some cases, supplementation as a preventive treatment is questionable [28,35,41,42].

Moreover, some patients were shown to display severe subacute or acute PN, with clinical course and features suggestive of idiopathic demyelinating polyneuropathy (Guillain-Barrè or CIDP-like forms), confirmed, in some cases, by the presence of inflammatory changes in cerebrospinal fluid and on nerve biopsy [35,43–46] (Table 2).

Even though co-occurrence of two unrelated conditions can't be excluded, the increased frequency of severe PN patients treated with CLDII versus oral LD opens the question whether high LD bioavailability or the route of administration might subtend this phenomenon. An hypothetical explanation might involve the triggering of a dysimmune process due to modifications in the intestinal microenvironment [35].

CLDII is an effective treatment for advanced PD, which is approved in Europe since 2004. A water-based suspension of LD/carbidopa in carboximethyl cellulose is administered by intrajejunal infusion. This treatment allows to bypass gastric emptying and improve absorption leading to more stable plasmatic levels compared to oral LD, and may therefore provide an improvement of motor fluctuations and dyskinesia [47]. Patients on CLDII generally reach higher daily doses compared to oral LD. Furthermore, they have usually been exposed to oral LD for years. Such features make these patients at higher risk of developing PN. Indeed, studies showed higher PN risk in CLDII patients compared to DA patients, whereas there was no statistically significant difference between CLDII and oral LD patients [25,35]. Nonetheless, Jugel et al. reported more severe neurographic abnormalities in CLDII compared to oral LD patients [48] (Table 2). The mechanism underlying PN in oral LD and CLDII patients is likely to be similar: a correlation between LD daily dose and PN occurrence has been observed in CLDII patients too [25,35] (Table 2).

Whilst long term follow-up studies confirmed CLDII efficacy in controlling motor symptoms, in 2007 the first case of acute PN during CLDII was reported [49] (Table 2).

In the following years, along with the increase in CLDII use, there have been other reports of acute/subacute PN, inconstantly associated with signs of encephalopathy [42–46] (Table 2). Some of these acute conditions were associated with severe weight loss and low micronutrients blood levels (vitamin B1, B6, B12, and folate) and improved after CLDII withdrawal with switch back to oral therapy and vitamin supplementation [35,42,50–52]. Other patients displayed clinical, neurophysiological and laboratory features of dysimmune demyelinating PN (Guillain-Barrè or CIDP-like forms). CSF examination showed albuminocytologic dissociation, and clinical improvement was observed with immunomodulatory therapy (corticosteroids, plasmapheresis, i.v. immunoglobulins) [35,46,49,53]. Acute forms appeared weeks/month after CLDII initiation [35,44–50].

Although rare cases of acute PN in patients on high doses of oral LD were reported, such pattern seems far more frequent in patients on CLDII [27,44,54] (Table 2).

Acute/subacte PN may be related to different, although potentially overlapping factors: i) Nutritional deficiency. Vitamin B deficiency, especially B6, may predispose to acute PN. There are several cases of acute PN reported in patients who underwent bariatric surgery [55]. Moreover, an interaction between gel and gastrointestinal function cannot be ruled out, and cases of malnutrition under CLDII were reported. We can speculate that the presence of gel might interfere with micronutrients absorption. Furthermore there is a potential interference with microbacterial growth, leading to malabsorption, as observed during enteral nutrition [56]; ii) Intestinal flora changes could also facilitate the proliferation of particular bacterial species (i.e. Campylobacter jejuni) known to trigger dysimmune reaction [57].

4. Open issues and controversies

The main problem in assessing the intrinsic contribution of PD to PN is that most patients are treated immediately after diagnosis. Accordingly, available epidemiological data were obtained in small groups of early PD patients, and no large case–control prospective study on the prevalence of PN in drug-naïve patients compared to controls can be performed. On these premises, it will be very difficult to dissect the role of disease evolution and aging form the effect of pharmacological treatment.

Studies from the pre-LD era do not indicate significant PNS dysfunction in PD but disease duration was short at that time and severe motor disability might have masked additional peripheral symptoms.

Since the discovery of LD in the 1960's, only recent reports have suggested increased frequency of PN in PD. A review of about 80 clinical trials comparing LD with placebo or other drugs, has been conducted by Teodoro et al. [58]: no PN cases where reported and symptoms suggestive of PN showed no significant inter-group difference. Moreover, a comprehensive analysis of pharmacovigilance data did not detect reports of PN associated with LD exposure. Nonetheless, clinical trials population is often not representative of the whole patient population and follow-up might have been too short to detect symptoms of PNS dysfunction. Finally, acute/subacute cases might have been under-reported because considered unrelated to therapy [59].

5. Conclusion

The relationship between PD and PNS dysfunction is still uncertain. There is increasing evidence pointing to a form of small fiber neuropathy intrinsic to PD and therefore not in strict relation to pharmacological treatment. On the other hand, medium-large fiber PN is also a relatively frequent and potentially severe complication in advanced LD-treated PD making it difficult to disentangle disease from treatment-related factors. A possible association with subclinical VB12 deficiency and hyperhomocysteinaemia related to LD intake exists and malnutrition and vitamin B group deficiency would favor acute PN and encephalopathy in CLDII patients.

To further elucidate the above mentioned issues, both early and advanced PD patients should be more strictly monitored for subtle neuropathic signs, nutritional and micronutrients status. Prospective data from cohort studies suggest that neurophysiological evaluation before CLDII and its periodical assessment during treatment helps detecting initial symptoms allowing potentially better management.

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