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Point of view

The peripheral nerve involvement in Parkinson Disease: A multifaceted phenomenon

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ABSTRACT

In the last decade the possible relationship between Parkinson's disease (PD) and peripheral neuropathy (PN) has received increasing attention.

Given that PN is quite common in Parkinson's disease, much controversy has arisen on whether it is part of the neurogenerative process itself - actually one of the possible causes - or a complication of levodopa administration.

In this article we will discuss the different hypotheses, as well as our perspective on these open issues.

The presence of peripheral neuropathy (PN) in the context of Parkinson Disease (PD) was traditionally considered of scarce epidemiologic relevance, limited to rare cases of Parkin mutations, mitochondrial disease with parkinsonism or families with parkinsonism-neuropathy syndromes [1]. The scenario has changed in the last decade since a large number of clinical-pathological studies detected on the one hand its frequent appearance in the late phase of the disease, in the context of long-term Levodopa (LD) exposure, on the other its detection at a very early stage (often preclinical), thus considering the peripheral involvement as an early step of neurodegeneration before it spreads to the CNS [2].

In the following sections we will analyze the many faces of this phenomenon and discuss their clinical implications and the related controversies which are still to be unraveled.

1. The first aspect (acquired neuropathy)

Several studies, all published after 2004 (Table 1), reported the occurrence of PN during long-term LD treatment.

Toth et coll pioneered this field. In their first study [4], they screened over 500 PD patients for "idiopathic" PN found in 34 cases, 32 of whom had abnormal serum levels of Vitamin B12 (VB12), Homocysteine (Hcy) and/or Methylmalonic acid (MMA).

In a subsequent study of the same group [5], PN was found in the remarkable percentage of 58% in 58 PD patients on LD (vs. 9% in controls) with positive correlation with UPDRS motor score, LD cumulative dose, high seric Hcy and MMA levels.

A high prevalence of PN was detected also in a subsequent case–control study published by Rajabally et al. [7]. In their sample, actually quite narrow (37 pt s vs. 37 controls), PN was identified in 38% of the PD group (vs. 8% controls) in association with VB12 deficiency, cumulative LD exposure and PD duration.

In 2013, a large Italian multicenter study, conducted on about 500 pt s, stratified the risk of neuropathy, based on the length of LD exposure [9]. The study showed a significant prevalence of PN in patients taking LD from a longer period (almost 20% in patients with LD exposure longer than 3 years vs 6.8% with shorter exposure and 4.8% LD free); the neuropathy also runs with the cumulative dose of LD, high Hcy and reduced VB12 serum levels.

The conversion of LD to dopamine requires a methyl group donation that is provided by adenosylmethionine. Such reaction leads to Hcy formation. Subsequent Hcy remethylation needs VB12 as co-factor, and alternative ways of degradation require methyl-entetrahydrofolate and pyridoxine (vitamin B6) [29,30]. The final result is that chronic LD intake leads to a sequence of events (Hcy accumulation and vitamin B6, VB12 and folate depletion) which alter peripheral nerve homeostasis.

Hcy can cause neurotoxicity through several mechanisms: by increasing vulnerability to mitochondrial toxins and rising free radicals, by inducing inflammatory reactions, and also by impairing DNA repair mechanisms [31–33]. LD-related increased Hcy was associated with signs of sural nerve axonal neurodegeneration in an electrophysiological study of patients with PD and healthy controls

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Table 1
Studies investigating determinants of PN in PD.

Authors	Determinant	Main findings
Muller et al. (2004) [3]	Oral LD	Axonal sensory PN in PD patients. ↑ Hcy
Antonini et al. (2007) [10]	LCIG	Subacute axonal PN
Toth et al. (2008) [4]	Oral LD	Axonal PN, ↓ vit B12, folate ↑ Hcy MMA
Manca et al. (2009) [11]	LCIG, Nitrous oxide inhalation	Acute axonal PN, encefalopathy ↑ Hcy, MMA, VB12 within the lower limit of normality
Toth et al. (2010) [5]	Oral LD	Axonal sensory PN, ↑ Hcy, MMA
Urban et al. (2010) [12]	LCIG	Subacute axonal PN
Gondim et al. (2010) [6]	Oral LD	Axonal PN
Rajabally et al. (2011) [7]	Oral LD	↓VB12
Santos-Garcia et al. (2011) [13]	LCIG	Subacute axonal PN
Meppelink et al. (2011) [14]	LCIG	Axonal sensory PN
Klostermann et al. (2012) [20]	LCIG	Subacute axonal PN
Galazky et al. (2013) [15]	LCIG	Mixed axonal-demyelinating PN
Jugel et al. (2013) [16]	LCIG, Oral LD	Axonal PN in both group (more severe in LCIG patients)
Kimber et al. (2013) [8]	Oral LD	Mixed (primary axonal/secondary demyelinating) PN
Ceravolo et al. (2013) [9]	Oral LD	Axonal predominantly sensory PN, ↓ VB12, ↑ Hcy
Merola et al. (2014) [17]	LCIG	Subacute axonal PN
Mancini et al. (2014) [18]	LCIG	Axonal PN in some cases, acute (GBS-like) PN in others
Uncini et al. (2014) [19]	LCIG	Acute (GBS-like) PN
Cossu et al. (submitted) [20]	Oral LD	Axonal sensory PN, protective effect of I-COMT
Nolano et al. (2008) [21]	Intrinsic	↓ of ENF and MC in PD patients
Ikemura et al. (2008) [22]	Intrinsic	α-syn in the skin of PD patients
Miki et al. (2010) [23]	Intrinsic	α-syn in the skin
Nolano et al. (2011) [24]	Intrinsic	↓ ENF in both treated and untreated patients, ↓ MC in treated patients only
Wang et al. (2013) [25]	Intrinsic	↓ IE, PM and SM fibers, ↑ α- syn in skin and nerves of PD patients
Donadio et al. (2014) [26]	Intrinsic	α-syn in skin of PD patients
Doppler et al. (2014) [27]	Intrinsic	α-syn in skin of PD patients
Zange et al. (2015) [28]	Intrinsic	α-syn in the skin of PD patients only

Abbreviation: LCIG: Levodopa-carbidopa intrajejunal gel; GBS: Guillain-Barre syndrome; Hcy: Homocysteine; MMA: Methylmalonic acid; PD: Parkinson's disease; PN: Peripheral neuropathy; VB12: vitamin B12; I-COMT: COMT inhibitors.; ENF: epidermal nerve fibers; IE: intraepidermal; LB: Lewy bodies; MC: Meissner corpuscles; PD: Parkinson's disease; PM: pilomotor; SM: sudomotor; MSA: Multi-system atrophy; ET: Essential tremor.

[3]. Furthermore, the role of high Hcy levels in inducing peripheral damage has been confirmed in diabetic neuropathy [34], in patients with 5,10-methylenetetrahydrofolate reductase deficiency [35] and in a longitudinal clinical and electrophysiological study conducted on a large group of elderly individuals [36]. VB12 deficiency, which is a well-known cause of reversible peripheral neuropathy in older adults [37,38], act through reduced SAM or elevated methylmalonic acid (MMA) levels. In most cases, as observed in our previous study [9], VB12 levels were significantly lower than those observed in healthy controls, yet they were not always totally deficient. This suggests that the neuropathic changes could be related to the exposure to toxic metabolites (Hcy, MMA) resulting from a combination of high LD concentration and cobalamin functional insufficiency, rather than VB12 deficiency per se.

In patients on oral LD, these metabolic changes leading to peripheral damage occur gradually, causing, in general, a mainly sensitive, usually mild, sometimes subclinical chronic PN. With the advent of a new formulation of enteral LD, the increased bioavailability and, possibly, the peculiar mode of administration, changed the clinical presentation of the LD-related PN with the observation of more severe acute/subacute forms, especially in the presence of simultaneous (other than LD) precipitating factors [10,11].

After these initial reports of severe subacute cases [10,11], numerous additional descriptions of chronic intestinal LD gel-related PN have followed [12–17,19]. In some of these cases, some mechanisms, different from that vitamin deficiency, have been hypothesized, in particular a Guillain-Barrè-like phenomenon caused by an immune reaction linked to the drug vehicle gel or by a C. Jejeuni increased risk of infection due to the chronic presence of the duodenal probe. However, to date, there is no ultimately evidence supporting a dysimmune/inflammatory or infectious genesis at the base of the intestinal LD gel-related PN.

In many cases, it seems possible to define the LD-linked PN spectrum as a continuum in pathogenesis, course and severity, with the enteral formulation ensuring greater drug bioavailability yet also facing an increased PN risk compared to oral therapy.

On the other hand, it was observed that the co-administration of ICOMT which, when taken for a sufficiently long period of time is effective in reducing serum levels of Hcy and preserving those of VB12 and folate, is able to significantly lower the development of neuropathies in PD patients with prolonged exposure of LD [Cossu et al., submitted]. Bearing in mind this assumptions, we recommend monitoring seric of Hcy and VB12 levels for patients with prolonged oral LD exposure but, above all, for those in infusional intestinal therapy, as well as periodic clinical and EMG assessment in order to detect early PN signs and set a ready supplementation therapy. The latter can also be pragmatically practiced beforehand: we suggest the empirical approach of VB12 1 fl (5000 mcg)/day for 7 days at the beginning of treatment and then follow with 1 fl/month as maintenance dose; folate administered in cycles with a daily dose of 5 mg.

Also, the use of ICOMT can be considered among the potential strategies of prevention of LD-related neuropathy, but it must be preceded by an accurate risks/benefits assessment for its ability to increase dyskinesias [39].

The VB6 supplementation is instead not recommended because it counteracts the action of decarboxylase inhibitor (which inhibite the peripheral conversion of the LD into dopamine).

2. The second aspect (intrinsic neuropathy)

Extrinsic neuropathy, often arisen in the advanced stage of the disease, is only one of the faces of peripheral involvement in PD. In many patients, in fact, it was possible to identify a mild subclinical neuropathy, independent of LD therapy, sometimes already present at an early stage of the disease so to consider the peripheral involvement as an early step of the neurodegeneration before it spreads to the CNS.