INVITED EDITORIAL

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Polyneuropathy and levodopa therapy in Parkinson's Disease: an evolving clinical challenge

Jarosław Dulski[1–3]

[1]Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland
[2]Neurology Department, St Adalbert Hospital, Copernicus PL Ltd., Gdansk, Poland
[3]Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by a combination of motor and non-motor symptoms that significantly impact the quality of life of patients [1–5]. Levodopa formulations with peripheral dopa decarboxylase inhibitors, such as benserazide or carbidopa, remain the gold standard treatment due to their effectiveness in replenishing striatal dopamine levels [6].

Traditionally administered orally, levodopa therapy has evolved to include intrajejunal and, more recently, subcutaneous delivery methods to better manage motor fluctuations and dyskinesias in advanced stages of PD [7].

An association between levodopa therapy and polyneuropathy was first observed in patients receiving high doses of oral levodopa [8]. The metabolism of levodopa and dopamine through catechol-O-methyltransferase leads to the production of homocysteine, a neurotoxic amino acid.

Remethylation of homocysteine back to methionine requires vitamin B12 and folate as essential cofactors. Alternatively, homocysteine can be converted to cystathionine through the transsulfuration pathway, which requires vitamin B6. In PD patients, increased levodopa intake elevates homocysteine levels, potentially depleting these vitamins and leading to deficiencies in folic acid, and vitamins B6 and B12 [8]. Elevated homocysteine levels and vitamin deficiencies have been implicated in the development of polyneuropathy. However, it remains unclear whether these factors alone or other mechanisms are primarily responsible for the neuropathy, suggesting a multifactorial etiology [9].

With the advent of levodopa-carbidopa intestinal gel (LCIG), concerns about polyneuropathy have resurfaced [10, 11]. Unlike the predominantly chronic and sensory polyneuropathy observed with oral levodopa intake [12], patients receiving LCIG can develop acute, subacute, and chronic neuropathic symptoms. The acute form is particularly concerning, as it is often disabling and leads to discontinuation of therapy. In the original paper by Havránková et al. [13] published in this issue, the authors report findings from a multicentre study examining the association between LCIG and acute polyneuropathy. They retrospectively evaluated 183 patients treated with LCIG across seven Czech and Slovak movement disorder centers and identified acute polyneuropathy in six patients. Discontinuation of LCIG in all six patients resulted in stabilization or improvement of their neuropathic symptoms.

Havránková et al. suspected two mechanisms involved in the pathophysiology of acute polyneuropathy in LCIG-treated patients: inherited (genetic) and acquired (e.g. autoimmune factors post-infection) predispositions, and the potential toxic effects of high doses of LCIG on the jejunum or directly on the peripheral nervous system [13].

The genetic landscape of both familial and sporadic PD is continuously evolving, and it is likely that certain genetic variants may influence an individual's susceptibility to developing polyneuropathy [14]. Genetic factors could modulate individual responses to levodopa and its metabolites, influencing the risk of neuropathy development. For example, polymorphisms in genes involved in homocysteine metabolism could predispose patients to higher homocysteine levels [15].

Furthermore, neuropathy could be related to autoimmune mechanisms, as seen in other autoimmune diseases that manifest with neuropathic symptoms [16]. Immune activation following infections could lead to an autoimmune response targeting peripheral nerves, resulting in neuropathy. Recently, attention has been given to atrophy of the vagus nerve in PD patients; however, whether this is part of the

Address for correspondence: Jarosław Dulski, Division of Neurological and Psychiatric Nursing, Medical University of Gdansk, Debinki 7 St., 80–211, Gdańsk, e-mail: jaroslaw.dulski@gumed.edu.pl
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neurodegenerative process or secondary to other insults is still unclear [17]. Some authors have argued that other causes have not been adequately ruled out, suggesting that sporadic diseases such as Guillain–Barré syndrome or chronic inflammatory demyelinating polyneuropathy could be contributing to the observed phenomena [18]. Lastly, the medication formulations for LCIG include additional ingredients, such as methylcellulose, which may have an impact on the gut microbiota and could potentially induce inflammatory bowel disease, thus indirectly affecting the nervous system [19].

It is important to note that in most patients, therapies with oral, intrajejunal, and subcutaneous levodopa formulations are well tolerated, and adverse effects are generally manageable. Supplementation with folic acid, vitamin B6 (not exceeding 25 mg per day), and vitamin B12 (avoiding cyanocobalamin in cases of renal impairment) is relatively safe in most cases, and can help mitigate neuropathy associated with hyperhomocysteinemia [8]. However, more information is needed to fully understand the mechanisms underlying acute polyneuropathy in patients treated with LCIG and to develop effective strategies for prevention and management. The introduction of subcutaneous foslevodopa/foscarbidopa as a novel treatment option adds another layer of complexity, as the frequency and risk of polyneuropathy associated with this therapy remain to be estimated.

Prospective studies involving larger cohorts and systematic monitoring of nutritional status, genetic factors, and immune markers are needed. Such research could provide valuable insights into the pathophysiology of neuropathy in PD patients and inform clinical practice to enhance patient outcomes. Addressing these gaps will be essential for optimising levodopa intrajejunal and subcutanous therapies and minimising their potential adverse effects.

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