

## Letter to the Editor: New Observation

# Oral Levodopa, Vitamin B6, and Polyneuropathy: A Case Series

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Vitamin B6 (pyridoxine) is essential for proper nerve function, and deficiency in this vitamin can lead to peripheral neuropathy.<sup>1</sup> In recent years, there have been several reports of patients with Parkinson's disease (PD) displaying coexisting peripheral polyneuropathy and B6 deficiency.<sup>2,3</sup> These cases suggest that B6 deficiency may contribute to the development or progression of polyneuropathy in PD patients. Levodopa is metabolized in the body by several enzymes, including aromatic L-amino acid decarboxylase and catechol-O-methyltransferase. Both enzymes require vitamin B6 as a cofactor to function properly.<sup>4</sup> As a result, levodopa therapy has been associated with decreased plasma levels of B6.<sup>3</sup> Here we present four cases of PD with peripheral polyneuropathy and B6 deficiency that presented to our clinic over a two-year period (Table 1). Through these reports, we hope to draw attention to this possibly under-reported clinical picture.

A 72-year-old woman developed PD in 2013 at the age of 65 (Case 1). She previously underwent DBS surgery in 2009 for severe essential tremor. In 2020, she reported numbness in all her fingers slowly progressing over the past twelve months. Physical examination did not reveal any significant abnormalities despite her subjective sensory complaints. Standard polyneuropathy workup only revealed borderline Hb1Ac (6,3%). The patient was already taking B12 supplements prior to the development of her symptoms. Vitamin B6 levels however were markedly low. No other cause could be identified to explain the patient's symptoms.

In 2019, a 79-year-old man with a diagnosis of PD for 15 years mentioned tingling in feet and fingers in the past 6 months (Case 2). Physical examination showed markedly reduced touch, pinprick, and pain sensation in all four extremities. Blood work initially showed mildly reduced vitamin B12 levels; therefore, supplementation with oral B12 was initiated. Six months later, the symptoms had not improved, leading to additional investigations. B6 levels were low, leading to supplementation with oral B6. No other cause could be identified to explain the patient's symptoms. It is interesting to mention this patient was initially taking hydralazine (30 mg daily), which has also been associated with B6 deficiency. Hydralazine was stopped when B6 deficiency was suspected.

A 69-year-old man was diagnosed with PD at the age of 51 and underwent DBS surgery at age 58 (Case 3). In 2018, he developed numbness and tingling in his fingers and feet. On examination, the

patient reported reduced sensitivity to touch and vibration at the ankle level. A year later, sensory abnormalities had progressed to knee level and the patient underwent NCS. Surprisingly, electrophysiologic parameters for the lower extremities were within normal limits. Vitamin B6 levels were markedly low. Again, no other cause could be identified to explain the patient's symptoms. Unfortunately, the patient's health and cognitive status deteriorated after contracting COVID-19, and clinical follow-up of the polyneuropathy was not possible before he passed away.

In 2020, a 81-year-old woman with a 13 years history of PD reported numbness in both feet (Case 4). Unfortunately, due to COVID restrictions, she could not travel to the clinic to be examined by a neurologist and NCS could not be performed. This patient had undergone NCS in 2018 in the context of L5 radiculopathy. This prior investigation had not shown abnormalities consistent with polyneuropathy, but it was before the symptoms developed. Blood work showed normal routine polyneuropathy workup but with low B6. At the follow-up phone appointment nine months later, she only complained of tingling in the right foot after pregabalin reduction, presumably due to her known L5 radiculopathy, but no physical examination could be done.

In these four patients treated with oral levodopa/carbidopa, peripheral polyneuropathy was found in association with vitamin B6 deficiency. There were no coexisting deficiencies in vitamin B12 in three of the four patients. The main limitations of this study are the lack of consistent follow-up as well as the absence of folate, homocysteine, and methylmalonic acid levels, which are also implicated in levodopa metabolism<sup>5</sup>. The fact that four patients presented within two years among the patients of a single treating neurologist raises the possibility that this condition is under-recognized in clinical practice. While there has been a growing concern regarding vitamin B6 deficiency and the risk of polyneuropathy in patients treated with levodopa/carbidopa intestinal gel (LCIG), our cases suggest a similar concern should be raised in patients treated with high doses of oral levodopa/carbidopa. Some experts recommend monitoring vitamin B6, B12, homocysteine, and methylmalonic acid in PD patients under treatment with LCIG<sup>6</sup>. We suggest such monitoring should also be recommended for patients on high doses of oral levodopa, especially if they describe symptoms suggestive of polyneuropathy.

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**Table 1:** Summary of laboratory, NCS assessment, and levodopa dosage

	At diagnosis			Treatment		Post-treatment	
	Plasma vitamin B6 (20–96 nmol/L)*	Plasma vitamin B12 (138–652 pmol/L)**	NCS	Oral levodopa dose (mg/day)	Oral B6 (mg)	Plasma vitamin B6 (20–96 nmol/L)*	Follow-up
Case 1	<10	584	Mild demyelinating sensory neuropathy, ulnar neuropathy	750	25 per day for 3 months followed by 50 per week	831	Complete resolution of symptoms after one year
Case 2	17	121	Mild sensory axonal polyneuropathy	1500	50 per day	140	No change in symptoms after 6 months
Case 3	<10	528	Axonal sensory polyneuropathy in upper extremities, moderate bilateral carpal tunnel syndrome	1850	25 per day for one month followed by 50, three times per week	–	–
Case 4	14	936	–	900	50 per week	60	Resolution of symptoms after 9 months

NCS: nerve conduction studies.

\*Normal local laboratory values for vitamin B6.

\*\*Normal local laboratory values for vitamin B12.

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**Statement of Authorship.** C.D. and M.B. designed the study. M.B. and G.L. were involved in data collection. C.D. drafted the manuscript and designed the tables and figures. M.B. and G.L. revised the manuscript.

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