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Prevalence of Levodopa-Induced Peripheral Neuropathy in Patients with Parkinson's Disease and Vitamin B12 Deficiency

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Abstract

Background: Parkinson's disease (PD) is one of the widespread neurodegenerative diseases. Recently, a few studies have suggested that treatment with levodopa and vitamin B12 deficiency may have some role in developing peripheral neuropathy (PN) among PD patients. Hence, the aim of this study was to evaluate PN in patients suffering from PD under long-term treatment with levodopa and also vitamin B12 deficiency in these patients. **Materials and Methods:** Thirty PD patients who received levodopa for at least two years, 30 levodopa-naïve PD patients, and 30 age-matched controls individuals were included. The participants were subjected to electrodiagnostic tests and the level of vitamin B12 was measured. The prevalence of neuropathy was determined according to electrodiagnostic criteria and compared among the three groups. **Results:** Overall, 23.3% of cases in levodopa receivers, 3.3% in the levodopa-naïve group, and 3.3% in control group had PN (odds ratio=8.8, 95% confidence interval=1.7-45.6). Levodopa group had significantly lower serum vitamin B12 than the other two groups ($P=0.006$). Vitamin B12 insufficiency was detected in 36.6% of patients in the levodopa group, which was significantly higher than other groups (23.3% in the levodopa-naïve and 6.6% in the control groups, $P=0.02$). A significantly negative correlation was noticed between the duration of levodopa exposure and serum level of vitamin B12 ($r=-0.31$, $P=0.016$). **Conclusion:** Our study demonstrated a significantly higher prevalence of vitamin B12 insufficiency and PN in PD patients under treatment with levodopa. Also, our results advocate the role of levodopa in PN development through the vitamin B12 derangement. [GMJ.2021;10:e1837] DOI:[10.31661/gmj.v10i0.1837](https://doi.org/10.31661/gmj.v10i0.1837)

Keywords: Parkinson's Disease; Peripheral Neuropathy; Levodopa; Treatment; Complication

Introduction

Parkinson's disease (PD) is characterized as a devastating neurologic disease that caus-

es motor function impairments such as bradykinesia and other symptoms such as dementia and sleeping problems. It affects 2-3% of the elderly population aged over 65 years [1]. It is

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reported one of the prevalent complications of this disease is peripheral neuropathy (PN) [2-7]. It is estimated that large fiber neuropathy occurs in over 16% of idiopathic PD [7]. The exact pathophysiology of PN in PD patients is yet to be determined; however, it is proposed by some studies that PN could be due to the long-term use of L-dopa (levodopa) [2-7]. Moreover, Toth *et al.* reported that over 90% of PD patients with PN had vitamin B12 deficiency. Accordingly, they suggested that PN in PD could be due to iatrogenic vitamin B12 metabolic abnormalities [6]. However, little evidence is available to determine the association of these factors with PN development in PD patients. Therefore, this study aimed to evaluate the prevalence of PN in patients suffering from PD and the role of vitamin B12 insufficiency and the use of levodopa medication in the development of PN.

Materials and Methods

This case-control study was performed on idiopathic PD patients who were referred to the Neurology Clinic of Imam Reza Teaching Hospital of Tabriz University of Medical Sciences, Iran. Out of these patients, those with systemic and endocrinology diseases, collagen vascular diseases, chronic infection, immunosuppressive status, autoimmune disorders, cancer, orthopedic surgery within the last six months, malabsorption syndromes (such as celiac disease), history of gastrectomy or atrophic gastritis, taking certain medications that interfere with the absorption of vitamin B12 (such as PPIs), potential risk factors for PN, received vitamin supplementations within the last six months, and alcohol and drug abuse were excluded. Thirty idiopathic PD patients under continuous treatment with levodopa for equal or more than two years (considered as long-term use) were randomly selected and included in this study. Thirty patients who had not received levodopa or had exposure for less than six months were randomly selected as levodopa-naïve PD patients. Thirty age-matched healthy subjects were recruited from Imam Reza Hospital's staff. All the participants received a general explanation regarding the aim of the study and research protocol, and each participant signed written informed

consent. The study protocol was confirmed by the Ethical Committee of Tabriz University of Medical Sciences (code=IR.TBZMED.REC.1394.1001). All the subjects' medical records were studied. A neurological examination was performed on each participant, including temperature and vibration sensation, pinprick sensation test, deep tendon reflexes (DTR), limb coordination, gait and Romberg test. Subjects then underwent an electromyography/nerve conduction velocity (EMG/NCV) study. EMG/NCV was performed using the Medelec Synergy electromyography instrument (VIASYS Healthcare, Surrey, UK). A modified form of total neuropathy score was used to determine the severity of the PN and PN parameters. The nerve conduction study consisted of nerve latency and amplitude tests on tibial, peroneal and sural nerves. Proximal tibial latency with stimulation at the popliteal fossa. Gastrocnemius H-reflex and F-wave proximal latency of the tibial nerve. The next day after the neurological evaluations of the participants, the level of vitamin B12 was measured by taking 20 ml of the brachial vein blood sample. Patients' demographic data, duration of levodopa exposure, age at the PD onset, total neuropathy score (TNS) and vitamin B12 levels were recorded. The sample size was calculated by Epi info v.7. The primary outcome of this study was PN. The two-sided confidence interval, power, and ratio (unexposed: exposed) were set at 95%, 85%, and 1, respectively. According to the study of Toth *et al.* the percent of purpose property in the unexposed group and odds ratio were determined as 9% and 12.4, respectively [5].

The statistical analysis was conducted by SPSS software version 19.0 (SPSS Inc., Chicago, USA). The effect of levodopa on PD was assessed by the odds ratio test. The correlation between levodopa and serum vitamin B12 level was determined by Pearson's test. The mean vitamin B12 level was compared between subjects using the ANOVA test. Data were presented as mean SD. A P-value less than 0.05 was considered as significant differences.

Results

During the study period, all 90 subjects com-

pleted the study. Patients' characteristics are demonstrated in Table-1. No significant difference was seen among study groups in terms of demographic characteristics, including age ($P=0.271$) and sex ($P=0.081$). Among included subjects in three groups, seven cases (23.3%) in the levodopa group, one case (3.3%) in the levodopa-naïve group, and one case (3.3%) in the control group had PN; corresponding to an odds ratio of 8.82 ($P=0.049$, 95% confidence interval [CI]: 1.7-45.6) for PN in PD patients who had long-term levodopa exposure as compared to healthy controls. The cor-

related odds ratio after corrections for the age was 7.6 ($P=0.018$, 95%CI: 1.42-40.63). The TNS results are shown in Table-2. The mean TNS was significantly greater in the levodopa exposure group than levodopa-naïve patients and healthy controls ($P=0.005$ for both).

A statistically significant correlation was detected between the duration of levodopa exposure and the severity of PN assessed by TNS ($r=0.51$, $P=0.001$, Figure-1). Among TNS parameters, DTR and motor symptoms were more affected by the levodopa administration (Table-2). Levodopa group had significantly

Table 1. General and Clinical Characteristics of the Participants.

Variables	Group			P-value
	Levodopa	Levodopa-naïve	Control	
Age, y (mean± SD)	65.46±6.98	63.2±6.68	62.53±8.15	0.271
Male/female ratio	16/14	20/10	17/13	0.081
Age at PD onset, y (mean ± SD)	57.96±5.90	60.1±6.75	N/A	0.141
Duration of levodopa administration, y (mean± SD)	5.96±2.55	0.33 ± 0.47	N/A	0.001
Vitamin B12 level, pg/mL(mean± SD)	219±79.06	268.63±80.75	278.46±65.23	0.006

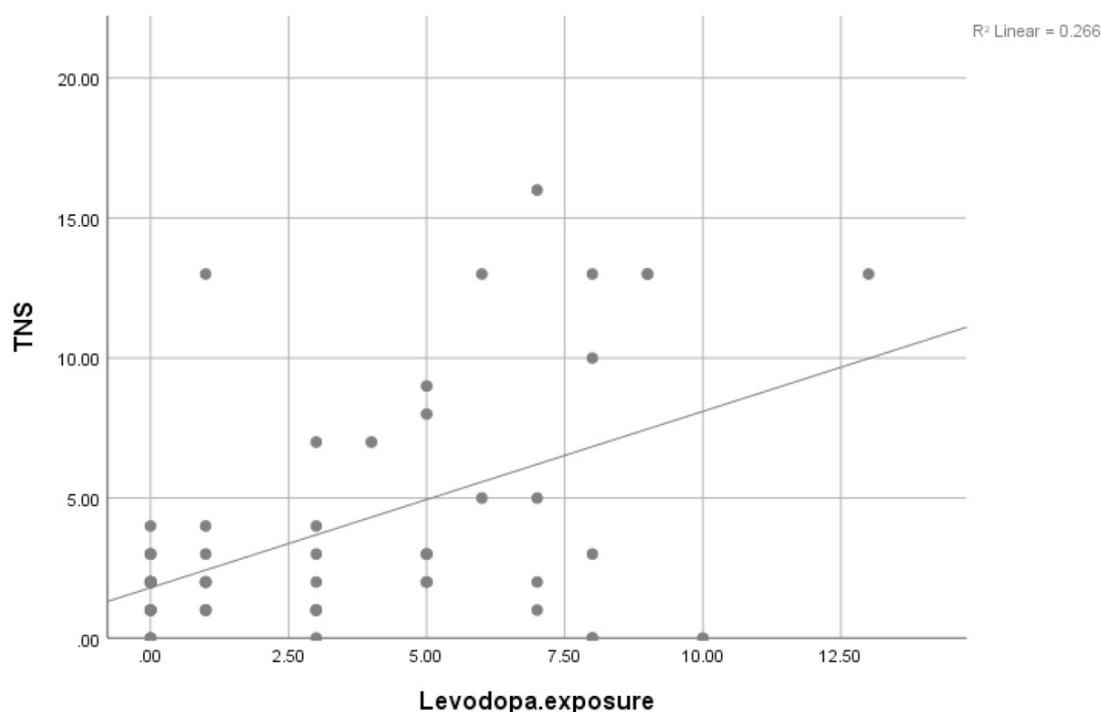


Figure 1. The linear regression between levodopa exposure and TNS. The long-term intake of levodopa increases the severity of neuropathy assessed by TNS.

lower serum vitamin B12 than the other two groups (219±79.06 pg/mL, 268.63±80.75 pg/mL, and 278.46±65.23 in levodopa exposure, levodopa-naïve and control groups, respectively, P=0.06). Vitamin B12 deficiency was detected in 36.6% of patients in the levodopa group, which was significantly higher than other groups (23.3% in the levodopa-naïve and 6.6% in the control groups, P=0.02). Moreover, a significant negative correlation was detected between the duration of levodopa exposure and serum vitamin B12 level (r=-0.31, P=0.016). The prevalence of vitamin B12 insufficiency was considerably higher in the levodopa group than in other groups when assessed separately among those with or with-

out PN (P=0.01 for both, Figure-2).

Discussion

In the current study, a considerable proportion of PD patients with long-term levodopa exposure had PN. They also had a lower level of serum vitamin B12. The higher prevalence of PN in PD patients was consistent with previous reports [3, 7]. Mancini *et al.* also reported that PD patients under treatment with intestinal or oral levodopa are at higher risk of PN development than other dopaminergic medications [3]. PD patients with short-term levodopa exposure had higher vitamin B12 levels and lower PD rates than long-term

Table 2. TNS Characteristics Among Three Study Groups

Groups		Sensory Symptoms (0-4)	Motor Symptoms (0-4)	Pin Sensibility (0-4)	Strength (0-4)	DTR (0-4)	QST Vibration Threshold (0-4)	TNS (0-24)
		Levodopa (n=30)	Median	0	2	1	1	1
	Range	0-3	0-3	0-3	0-3	0-3	0-3	0-16
	Mean	0.7±1.5	1.03±1.09	0.96±0.88	0.66±0.84	1.1±1.02	0.86±0.86	5.33±4.95
Levodopa-naïve (n=30)	Median	0	1	1	1	0	0	2
	Range	0-2	0-3	0-2	0-2	0-2	0-2	0-13
	Mean	0.06±0.361	0.73±0.69	0.63±0.55	0.4±0.56	0.23±0.56	0.16±0.46	2.23±2.23
Control (n=30)	Median	0	0	1	0	0	0	1.5
	Range	0-3	0-3	0-2	0-3	0-3	0-2	0-16
	Mean	0.16±0.59	0.4±0.72	0.6±0.56	0.36±0.66	0.2±0.61	0.46±0.57	2.2±3.85
P-value	ANOVA	0.002*	0.020*	0.79	0.19	0.001*	0.001*	0.001*

*Significant difference between mean results (P<0.05)

**Higher scores are representative of poorer function in each test.

DTR: Deep tendon reflex; TNS: Total neuropathy score

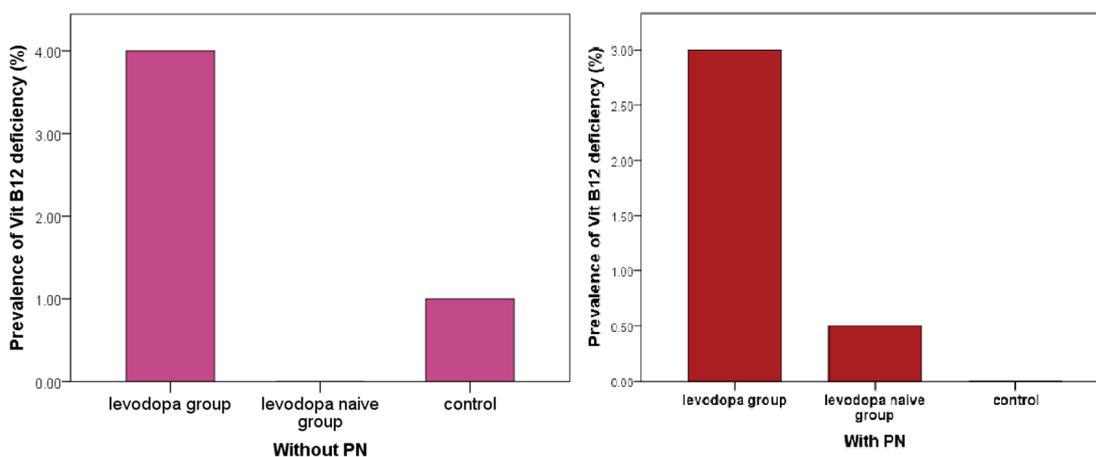


Figure 2. Prevalence of vitamin B12 deficiency among those with and without peripheral neuropathy (PN) in study three groups.

levodopa users. One of the possible mechanisms for PN in long-term levodopa takers could be its effect on the metabolism of vitamin B12. Some studies have suggested that PN in levodopa treated patients may be due to the neurotoxic accumulation of homocysteine and nitrite along with the vitamin B12 deficiency [8, 9]. There is no definite physiologic explanation for the association of vitamin B12 and levodopa metabolism. There is also some evidence that advocates the role of some genetic variations in PN progression in PD patients [8]. The levodopa-related metabolic toxicity is also associated with the depletion of vitamin B6 and elevation of methylmalonic acid [10-13].

Moreover, our study results demonstrated that the duration of levodopa administration was correlated with both severity of PN and lower vitamin B12 levels. Thus, levodopa accumulation seems to have a role in vitamin B12 derangement in PD patients. Toth *et al.* have shown that intramuscular injection of vitamin B12 can improve PN symptoms in PD patients with long-term levodopa exposure [5]. Mancini *et al.* suggested that vitamin B12/homocysteine level as a predictor of the development of PN in levodopa-user PD patients [3]. They indicated that the vitamin-associated axonal degeneration and the chronic inflammatory process might interplay with PN progression [7]. Ceravelo *et al.* also suggested the possible role of aging in PN development in PD patients [2]. In our study, even after the correlation for age, levodopa exposure increased PN chance in PD patients. However, the findings of Panagiotis *et al.* are inconsistent with our findings. They suggested that the increased prevalence of PN in PD patients is directly linked to vitamins and MMA rather than levodopa intake [14].

In this study, we used TNS for the evaluation of PN severity. This was the first study to use TNS for the evaluation of PN in PD patients. The findings of TNS were in line with EMG/NCV diagnosis; however, it provided a better quantification of the PN severity. EMG/NCV is a valuable tool for studying sensory and motor conduction and amplification in large myelinated nerves [15]. While nerve conduction studies are more subjective rather than objective. TNS provides a more precise eval-

uation of PN and is an appropriate modality for the classification of neuropathy severity [16]. It was first introduced to evaluate PN in chemotherapy-induced PNs but then became more popular in other fields, too [16-18]. Sadyk *et al.* evaluated vincristine-induced PN in patients with leukemia using TNS [19]. Moreover, in the study of Ghoeshi *et al.*, paclitaxel-induced PN was assessed in patients with breast cancer using TNS [20].

Nerve conduction studies are representative of the involvement of large sensory nerves in PD patients [21]. However, among TNS parameters in our study, DTR and motor symptoms were more affected by the levodopa administration. Romagnolo *et al.* reported small-fiber neuropathy in skin biopsy of PD patients suggesting the presence of PN before its detection by nerve conduction test [22].

Our study had several limitations. Due to the relatively small sample size, the prevalence of PN in PD patients cannot be generalized to the population of PD patients. The unblinded assessment for neuropathy could be considered as a source of bias. However, true blinding was not feasible in this setting because of the clinically obvious appearance of PD. Moreover, a longitudinal study design could be more helpful for enabling us to comment with more certainty on the causative relationship between levodopa, vitamin B12 deficiency, and PN in PD patients.

Conclusion

PN was more prevalent among patients who are suffering from PD and under long-term treatment with levodopa. Moreover, our results advocate the idea that one of the possible mechanisms underlying the levodopa-induced PN could occur through the deregulation of vitamin B12.

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Conflict of Interest

None.

References

- Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J et al. Parkinson disease. *Nat Rev Dis Primers*. 2017;3(1):17013.
- Ceravolo R, Cossu G, Bandettini di Poggio M, Santoro L, Barone P, Zibetti M et al. Neuropathy and levodopa in Parkinson's disease: evidence from a multicenter study. *Mov Disord*. 2013;28(10):1391-7.
- Mancini F, Comi C, Oggioni GD, Pacchetti C, Calandrella D, Moja MC et al. Prevalence and features of peripheral neuropathy in Parkinson's disease patients under different therapeutic regimens. *Parkinsonism Relat Disord*. 2014;20(1):27-31.
- Müller T, van Laar T, Cornblath DR, Odin P, Klostermann F, Grandas FJ et al. Peripheral neuropathy in Parkinson's disease: levodopa exposure and implications for duodenal delivery. *Parkinsonism Relat Disord*. 2013;19(5):501-7.
- Toth C, Breithaupt K, Ge S, Duan Y, Terris JM, Thiessen A et al. Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease. *Ann Neurol*. 2010;68(1):28-36.
- 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;23(13):1850-9.
- Zis P, Grünewald RA, Chaudhuri RK, Hadjivassiliou M. Peripheral neuropathy in idiopathic Parkinson's disease: a systematic review. *J Neurol Sci*. 2017;378:204-9.
- Brattström L. Plasma homocysteine and MTHFR C677T genotype in levodopa-treated patients with PD. *Neurology*. 2001;56(2):281-2.
- 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;100(35):2674-7.
- Rajabally YA, Martey J. Neuropathy in Parkinson disease: prevalence and determinants. *Neurology*. 2011;77(22):1947-50.
- Müller T, Renger K, Kuhn W. Levodopa-associated increase of homocysteine levels and sural axonal neurodegeneration. *Arch Neurol*. 2004;61(5):657-60.
- Urban PP, Wellach I, Faiss S, Layer P, Rosenkranz T, Knop K et al. Subacute axonal neuropathy in Parkinson's disease with cobalamin and vitamin B6 deficiency under duodopa therapy. *Mov Disord*. 2010;25(11):1748-52.
- Klostermann F, Jugel C, Müller T, Marzinzik F. Malnutritional neuropathy under intestinal levodopa infusion. *J Neural Transm*. 2012;119(3):369-72.
- Bargiotas P, Konitsiotis S. Levodopa-induced dyskinesias in Parkinson's disease: emerging treatments. *Neuropsychiatr Dis Treat*. 2013;9:1605.
- Domkundwar S, Autkar G, Khadilkar SV, Virarkar M. Ultrasound and EMG-NCV study (electromyography and nerve conduction velocity) correlation in diagnosis of nerve pathologies. *J Ultrasound*. 2017;20(2):111-22.
- Smith EML, Beck SL, Cohen J. The total neuropathy score: a tool for measuring chemotherapy-induced peripheral neuropathy. *Oncol Nurs Forum*. 2008;35:96.
- Wampler MA, Miaskowski C, Hamel K, Byl N, Rugo H, Topp KS. The modified total neuropathy score: a clinically feasible and valid measure of taxane-induced peripheral neuropathy in women with breast cancer. *J Support Oncol*. 2006;4(8):W9-W16.
- Gilchrist LS, Tanner L. The pediatric-modified total neuropathy score: a reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. *Support Care Cancer*. 2013;21(3):847-56.
- Sajdyk T, Boyle F, Foran K, Tong Y, Pandya P, Smith E et al. NTOX-12. OBESITY AS A POTENTIAL ATTRIBUTE FOR VINCRISTINE INDUCED PERIPHERAL NEUROPATHY. *Neuro-oncology*. 2017;19(Suppl 6):vi167.
- Ghoreishi Z, Keshavarz S, Asghari Jafarabadi M, Fathifar Z, Goodman KA, Esfahani A. Risk factors for paclitaxel-induced peripheral neuropathy in patients with breast cancer. *BMC Cancer*. 2018;18(1):958.
- Huynh W, Kiernan MC. Nerve conduction studies. *Aust Fam Physician*. 2011;40(9):693.
- Romagnolo A, Merola A, Artusi CA, Rizzone MG, Zibetti M, Lopiano L. Levodopa-Induced Neuropathy: A Systematic Review. *Mov Disord Clin Pract*. 2019;6(2):96-103.