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Clinical and laboratory status in Parkinson's disease patients with and without polyneuropathy

Klinička i laboratorijska slika obolelih od Parkinsonove bolesti sa i bez polineuropatije

Sanela Popović*†, Nemanja Popović†, Dragica Hajder†, Smiljana Kostić‡, Aleksandra Lučić Prokin*†

***University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; †University Clinical Center of Vojvodina, Clinic for Neurology, Novi Sad, Serbia; ‡Military Medical Academy, Neurology Clinic, Belgrade, Serbia**

Abstract

Background/Aim. The etiology of polyneuropathy (PNP) in patients with Parkinson's disease (PD) is unclear, and there is a possible association between levodopa therapy, hyperhomocysteinemia, and PNP development due to methylation processes involving vitamin B12 and folic acid. The aim of this study was to analyze the difference in clinical presentation and disease severity between PD patients with and without PNP and to evaluate blood levels of vitamin B12, homocysteine, and folic acid in these patients. **Methods.** This cross-sectional study included 200 consecutive patients diagnosed with PD, divided into two groups: those with PNP and those without PNP. Diagnosis of PNP was confirmed by electromyoneurography. The first group consisted of 50 patients with PD with confirmed PNP, and the second 50 patients with PD without PNP. All patients were receiving levodopa therapy. Laboratory tests analyzed vitamin B12, folic acid, and homocysteine levels. **Results.** Patients with PNP were older when PNP was diagnosed (71 vs. 66 years, $p < 0.0001$), without differences in duration of levodopa therapy ($p = 0.359$) or daily dose ($p = 0.442$), and with significant motor impairment according to Unified Parkinson's Disease Rating Scale III ($p = 0.017$). No difference was found between groups for vitamin B12 ($p = 1.0$), folic acid ($p = 0.124$), and homocysteine ($p = 0.313$) serum levels. **Conclusion.** PD patients with PNP have a more pronounced motor deficit, while differences in vitamin B12, homocysteine, and folic acid values compared to the group without PNP were not registered.

Key words:
age factors; levodopa; parkinson's disease; polyneuropathies; severity of illness index; vitamin b 12.

Apstrakt

Uvod/Cilj. Etiologija polineuropatije (PNP) kod Parkinsonove bolesti (PB) je nejasna, a moguća je povezanost između terapije levodopom, hiperhomocisteinemije i razvoja PNP zbog procesa metilacije, koji uključuje vitamin B12 i folnu kiselinu. Cilj rada bio je da se utvrdi razlika u kliničkoj prezentaciji i težini bolesti između obolelih od PB sa i bez PNP, kao i da se proceni nivo vitamina B12, homocisteina i folne kiseline u krvi ovih bolesnika. **Metode.** Studijom preseka analizirano je 200 konsekutivnih bolesnika sa dijagnozom PB, podeljenih u dve grupe: bolesnici sa PNP i oni bez PNP. Dijagnoza PNP potvrđena je elektromioneurografijom. Prvu grupu činilo je 50 bolesnika obolelih od PB sa potvrđenom PNP, a drugu 50 bolesnika obolelih od PB bez PNP. Svi bolesnici bili su na terapiji levodopom. Laboratorijskim testovima analizirani su nivoi vitamina B12, folne kiseline i homocisteina. **Rezultati.** Bolesnici sa PNP bili su stariji u momentu postavljanja dijagnoze PNP (71 vs. 66 godina, $p < 0{,}0001$), bez statistički značajnih razlika u dužini uzimanja ($p = 0{,}359$) ili dnevnim dozama levodope ($p = 0{,}442$) i sa statistički značajno izraženijim motornim deficitom prema *Unified Parkinson's Disease Rating Scale III* ($p = 0{,}017$). Nisu nađene razlike između grupa za nivoe vitamina B12 ($p = 1{,}0$), folne kiseline ($p = 0{,}124$) i homocisteina ($p = 0{,}313$) u serumu. **Zaključak.** Bolesnici oboleli od PB sa PNP imaju izraženiji motorni deficit, dok razlike u vrednostima vitamina B12, homocisteina i folne kiseline u odnosu na grupu bez PNP nisu registrovane.

Ključne reči:
životno doba, faktor; levodopa; parkinsonova bolest; polineuropatije; bolest, indeks težine; vitamin b12.

Correspondence to: Sanela Popović, University Clinical Center of Vojvodina, Clinic for Neurology, Hajduk Veljkova 1, 21 137 Novi Sad, Serbia. E-mail: sanela_bozic@yahoo.com

Introduction

Parkinson's disease (PD) is a significant cause of disability in the elderly population with a trend of increasing incidence and mortality [1]. Considering the aging of the population as a global phenomenon, it is predicted that by the year 2040, the number of people suffering from PD will exceed 17 million [2]. According to studies covering the last three decades, the incidence of PD is related to age and increases proportionally in both sexes over the age of 65. A higher incidence was recorded in males, and a significant growth trend in both genders was observed in patients over 80 years of age [3, 4].

PD primarily affects parts of the central nervous system (CNS), leading to motor symptoms such as tremor, rigidity, bradykinesia, and postural instability [5]. In addition to motor symptoms, PD is also characterized by non-motor symptoms that include cognitive impairment, mood disorders, sleep disturbances, autonomic dysfunction, and sensory deficits [6]. While PD primarily involves the CNS, some reports and studies suggest that patients with PD may also present with peripheral neuropathies [7–9]. Polyneuropathy (PNP) refers to damage or dysfunction of peripheral nerves that can affect sensation, movement, and organ function. Common symptoms of PNP include numbness, tingling, weakness, pain in the hands and feet, and postural instability [10]. However, the exact relationship between PD and PNP is not fully understood and may involve multiple factors like medication side effects and age-related factors [8, 11].

PNP is an underestimated and often underdiagnosed comorbidity in patients with PD. The prevalence of PNP in patients with PD varies significantly and depends largely on the diagnostic protocols. In one of the earlier studies, Toth et al. [7] reported an incidence of PNP up to 55%. In a study published in 2008 [8], PNP was found in 69% of PD patients, while a significantly lower prevalence of 9.53% was recorded in an Indian cohort [12]. In these studies, the investigated PNP was found to be idiopathic.

The debate about the etiopathogenesis of PNP in PD markedly took place during the last decade. Several authors emphasized evidence of the possible neurotoxicity of levodopa, which leads to the occurrence of PNP in patients suffering from PD [8].

Patients on long-term levodopa therapy may exhibit increased plasma homocysteine and reduced serum vitamin B12 levels. This elevation is primarily due to the metabolism of levodopa by the enzyme catechol-O-methyltransferase (COMT) [13]. COMT activity necessitates the presence of certain vitamins, particularly B12, B6, and folic acid, which act as essential cofactors. During the breakdown of levodopa, methyl groups, which are integral to numerous biological processes, are depleted, leading to an accumulation of homocysteine. Under normal physiological conditions, homocysteine is recycled into methionine, a crucial amino acid, through a process requiring vitamin B12 and folate. Vitamin B6 plays a pivotal role in converting homocysteine into other non-toxic metabolites. A deficiency in these vitamins can thus impair the conversion process, resulting in elevated homocysteine levels [14]. This mechanism is also confirmed by the analysis of PD patients who used COMT inhibitors [15]. These drugs stop the methylation of levodopa, and thus, the toxic effects of hyperhomocysteinemia on peripheral nerve fibers and the development of PNP are absent. Certain authors also pointed to the correlation between the duration of exposure to levodopa, the daily dose of levodopa, and the risk of developing PNP [16].

Additionally, alpha-synuclein, as the main pathoanatomical substrate in PD, was detected in the peripheral nerve fibers of the skin, submandibular salivary glands, and the enteric nervous system [17, 18]. A study conducted by Finnish authors confirmed the presence of alpha-synuclein in the peripheral nerve fibers of the skin and sensory PNP in 50% of subjects. The authors were not able to confirm the association between alpha-synuclein and sensory PNP with a cumulative dose of levodopa and vitamin B12 hypovitaminosis, which would suggest that the development of PNP in PD is caused by neurodegeneration *per se* and not toxic effects of levodopa [18].

Neurological status in PD patients with and without PNP demonstrates significant heterogeneity. Various studies have suggested that the presence of PNP in patients with PD is associated with worse motor symptoms [11, 19]. However, other studies have not found a statistically significant difference in motor symptom severity between PD patients with and without PNP [9, 20, 21].

The aim of this study was to determine differences in the neurological status of PD patients with and without PNP, as well as to analyze the potential association of vitamin B12, folic acid, and homocysteine levels in PD patients with and without PNP.

Methods

This cross-sectional study was conducted in a five-year period, from January 1, 2018, until December 31, 2023, including two hundred patients with PD (aged 60–80 years) who were consecutively included during hospitalization and outpatient visits at the Neurology Clinic and Specialist Polyclinic, University Clinical Center of Vojvodina, Serbia. The research was approved by the Ethics Committee of the University Clinical Center of Vojvodina (No. 00-246/2022).

The study patients were diagnosed with PD according to the United Kingdom PD Society Brain Bank diagnostic criteria [22].

Clinical research included a collection of sociodemographic indicators, an assessment of the clinical characteristics of PD, a scale for assessing the neurological and functional status of patients with PD [Movement Disorders Society (MDS) Unified PD Rating Scale (UPDRS) – MDS-UPDRS] [23, 24, 25] symptoms and signs of PNP and electromyoneurography (EMNG). A five-channel device (Natus Neurology Inc., USA, 2014) was used for EMNG analysis. The electroneurography of the sensory nerves included the examination of the *nervus suralis*, *nervus peroneus superficialis*, *nervus ulnaris*, and *nervus radialis*. The Hoehn and Yahr scale, part of MDS-UPDRS, was used to evaluate the disease stage [25].

Exclusion criteria included a history of significant psychiatric diseases and dementia.

In the presence of symptoms and signs of PNP, EMNG was performed. The diagnosis of PNP was subsequently confirmed by EMNG. All patients were receiving levodopa therapy. The presence of other therapies for PD was not an exclusion criterion.

The included patients underwent laboratory tests to rule out other known causes of PNP. Blood samples were analyzed at the Center for Laboratory Testing, University Clinical Center of Vojvodina. Laboratory analyses included: complete blood cell count, renal functional test, liver function tests, fasting blood glucose and hemoglobin A1c, serum protein electrophoresis, test for inflammation (c-reactive protein) and autoimmunity (antinuclear antibody, rheumatoid factor, anti-neutrophil cytoplasmic antibody), thyroid function test (thyroxine, triiodothyronine, thyroid-stimulating hormone), and test for infectious disease screening (human immunodeficiency virus – HIV, hepatitis B, hepatitis C, Lyme disease, syphilis serology). Patients with previously known hereditary, metabolic (including diabetes mellitus), toxic, inflammatory, and/or autoimmune PNPs were also not included, nor were patients with confirmed severe radiculopathies and plexopathies.

Based on clinical findings, medical history, and also EMNG findings, all patients were categorized into two groups: those with PD and PNP (50 patients) and those with PD without PNP (50 patients).

In all PD patients with and without PNP, laboratory analyses also included the levels of vitamin B12, folic acid, and homocysteine. The normal serum values of homocysteine, vitamin B12, and folic acid were 5.1–15.4 μmol/L, 138.0–652.0 pmol/L, and 7.0 to 45.3 nmol/L, respectively.

Finally, this study included 100 patients diagnosed with PD according to the United Kingdom PD Society Brain Bank diagnostic criteria [22], who were able to understand the text of the informed consent and sign it voluntarily.

The data collected were entered into the database using the Excel for Windows. The descriptive statistical method, including arithmetic mean, standard deviation, and parameters indicating the shape of the distribution, was applied to describe the relevant values of continuous measures. The frequency method was applied to describe the categorical variants, which are relevant for describing the sample of patients and answering the research hypothesis. Pearson's correlation coefficient was used to examine the connection between continuous variants.

Pearson's Chi-squared test was applied when the difference in the frequency of responses to two categorical variables was examined, while the Mann-Whitney *U* and *t*-tests were used for continuous measures for non-dependent samples. The Mann-Whitney *U* test was used when the dependent variable was continuous and deviated from the normal distribution or when the measurement level of the dependent variable was ordinal. The *t*-test for dependent samples was applied when the dependent variable belonged to an interval measurement with normal distribution.

Results

The clinical and demographic characteristics of the examined groups are presented in Table 1. Most of the patients in both groups were male, but the differences between the groups of patients with PNP and without PNP did not reach statistical significance. There was no difference between the group's stages of the disease and disease severity, daily doses of levodopa, as well as the duration of levodopa administration. The group of subjects with associated PNP included older subjects (during the clinical examination of the patient when PNP was diagnosed), more

Table 1

Descriptive statistical indicators for Parkinson's disease patients in relation to the presence or absence of polyneuropathy (PNP)

Parameter	With PNP	Without PNP	*p*-value
Gender, n (%)			
male	41 (57.7)	20 (69.0)	0.297
female	30 (42.3)	9 (31.0)	
Age, mean (SD)	71.77 (5.05)	66.41 (6.13)	0.000*
[1]HY, n (%)			
I	4 (5.6)	2 (6.9)	0.082
II	30 (42.3)	20 (69.0)	
III	33 (46.5)	6 (20.7)	
IV	4 (5.6)	1 (3.4)	
Levodopa (month), mean (SD)	38.58 (28.58)	44.76 (34.76)	0.359
Levodopa daily dose, mean (SD)	360.56 (160.56)	393.10 (251.68)	0.442
Levodopa monotherapy, n (%)	53 (74.6)	13 (44.8)	0.004*
Levodopa + dopa agonist, n (%)	18 (25.4)	16 (55.2)	0.046*
MDS-UPDRS, mean (SD)			
I	9.90 (5.4)	9.55 (3.61)	0.749
II	13.30 (6.46)	13.14 (4.63)	0.905
III	35.39 (12.68)	29.45 (10.94)	0.017*
main score	58.68 (21.6)	52.52 (12.93)	0.155

HY – Hoehn and Yahr rating scale; MDS-UPDRS – Movement Disorder Society Unified Parkinson's Disease Rating Scale; SD – standard deviation; n – number. ****p* **– value reaches statistical significance.

[1]Note: For details on the scale used, see reference 22.

Table 2

Vitamin B12, homocysteine, and folic acid levels and the presence of polyneuropathy (PNP) in patients with Parkinson's disease

Parameter	PNP		*p*-value (χ^2 test)
	no	yes	
Folic acid			
normal	48	44	
high	0	4	0.124
low	2	2	
Vitamin B_{12}			
normal	49	49	
high	0	0	1.000
low	1	1	
Homocysteine			
normal	32	27	
high	17	23	0.313
low	1	0	

Results are given as number of patients.

frequent on levodopa monotherapy (74.6%), and they had more pronounced motor symptoms of PD (motor part, MDS-UPDRS III score).

Considering the relationship between the levels of folic acid, vitamin B12, and homocysteine, no significant differences were registered between the studied groups (Table 2).

Discussion

In our study, patients with PD who also had PNP did not differ significantly from those without PNP in terms of gender, stage of disease, and daily doses of levodopa, as well as the duration of levodopa administration. However, they exhibited significant differences in the motor component of the MDS-UPDRS. Patients with PD and PNP were frequently receiving levodopa therapy. Among the cohort of patients with both PD and PNP, male gender was more prevalent.

The authors of several recent studies similar to our sample report a male prevalence of up to 62% [26 - 28]. There are several hypotheses to explain this gender difference in patients with PNP. A higher incidence of PD in men has been recognized in all age groups [4, 5]. The influence of social and behavioral factors and different exposure to potential harmful noxes, i.e., higher exposure of the male sex to toxins, trauma, etc., are also mentioned [29]. It is presumed that the higher incidence of PNP in men is both because of biological/hormonal differences and different environmental influences [30]. Thus, in a recent study, Cardinez et al. [31] confirmed a higher frequency of PNP in men, while women more often reported symptoms of neuropathic pain.

By analyzing the subjects who have PD with associated PNP in our research, it can be concluded that these were older patients at the moment of examination. PD patients used levodopa monotherapy more frequently, and there is statistical significance between the groups. PD patients had higher motor test scores, i.e., worse neurological motor deficits. A more pronounced neurological deficit in patients with PD and PNP (when the study was conducted), a higher average age of these subjects as well as a later stage of the disease were also reported in other studies [19, 32]. The structure of the studied groups also indicates that the incidence of PNP increases with age [33].

The etiopathogenesis of PNP in PD is still unknown. Numerous studies have provided evidence of the toxic effects of levodopa [7, 8]. In recent decades, the role of alpha-synuclein and neurodegeneration in the etiopathogenesis of PNP in PD has been increasingly reported [18].

In this study, no significant statistical association was confirmed between the levels of vitamin B12, homocysteine, and folic acid and the presence of PD. However, in the available literature, there was no study with significant homogeneity of the obtained results.

The first significant study on the relationship between the cumulative daily dose of levodopa, the duration of exposure to levodopa, and the toxic effect of homocysteine was published in 2008 by Toth et al. [8]. The results of the study showed an increase in the value of homocysteine, which correlated with the cumulative dose of levodopa in subjects with PD associated with PNP. It was also concluded that there was no significant association between the values of vitamin B12 and PNP. Compared to our research, subjects included in the study by Toth et al. [8] were older, with a longer duration of PD and a higher cumulative dose of levodopa. Contrary to this study, a group of researchers from India found a low but still positive statistical association between the duration of the disease and hyperhomocysteinemia and a low but negative association between the reduction of B12 levels and the duration of the disease [12]. There was no statistically significant association with cumulative levodopa doses. In their sample, only 7.23% of subjects suffering from PD were diagnosed with PNP, and a non-significant association between PNP and hypovitaminosis B12, low folate level, and hyperhomocysteinemia was verified.

Ceravolo et al. [11] proved a statistically significant association between the duration of exposure to levodopa and the cumulative dose of levodopa and the occurrence of PNP, while a similar association could not be confirmed for the duration of PD. They also showed a positive statistical association with low levels of B12 and elevated homocysteine in

PD with PNP. Andréasson et al. [34] did not find an association between the cumulative daily dose of levodopa and PNP in PD. However, a strong positive association was identified between the PNP assessment scale score and hyperhomocysteinemia.

The authors of the meta-analysis published in 2023 point out that patients with PD may have elevated homocysteine values and decreased vitamin B12 values compared to healthy subjects and that the mechanism of PNP in PD is probably multifactorial [35]. In contrast to our results, the authors indicate that cumulative doses of levodopa and the duration of exposure to levodopa may contribute to the development of PNP, that hypovitaminosis B12 may be in a negative statistical relationship with the duration of PD and the stage of the disease, and that hyperhomocysteinemia can be correlated with the frequency of PNP in PD. From all that has been said, it can be concluded that PNP in PD is the result of complex mechanisms, both external and internal, which require additional research.

In our study, significantly higher values of the total MDS-UPDRS III score were recorded in patients with PNP. In contrast, in research published by Corrà et al. [9], differences between PD patients with and without PNP were not registered. The research of Schindlbeck et al. [36] was conducted on 39 newly diagnosed patients with PD who had not previously received levodopa therapy (levodopa naive patients) and also did not have a significantly higher MDS-UPDRS III score.

A group of American authors got similar results by analyzing gait in patients with PD with and without PNP, grouped according to disease duration and Hoehn and Yahr stage. Significant differences in the total MDS-UPDRS III score between groups were not recorded, although significantly slower gait, shorter step length, and greater variability of the step length were registered in patients with PNP [21].

In a recent study, Kühn et al. [19] analyzed motor and non-motor symptoms of PD in patients with PNP using both EMNG and high-resolution ultrasound in addition to a neuropathy questionnaire. Compared to our study, these patients were younger and in a later stage of the disease, and the MDS-UPDRS III score was lower for patients with PNP. Despite these differences, a positive correlation was found between the severity of symptoms of PNP and the values of the total MDS-UPDRS III score.

Our study has some limitations. First, a larger sample would be necessary for a complex or causal interpretation of the obtained results. The research was conducted as a cross-sectional study, which included a selected sample of PD patients with PNP. However, the analyzed subjects do not represent an objective sample from the tertiary health center. Second, other methods, such as skin biopsy, are necessary to achieve reasonably high sensitivity in diagnosing PNP, especially small-fiber PNP in PD patients. Yet, due to its invasive approach and high requirements, EMNG used in this study is still considered the most widely used method.

Conclusion

Our study shows that polyneuropathy in Parkinson's disease is more often diagnosed in older patients and is associated with the worse motor status established by the MDS-UPDRS III score. Low levels of serum vitamin B12, folic acid, and hyperhomocysteinemia were not associated with the presence of polyneuropathy in patients with Parkinson's disease.

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