Peripheral Neuropathy in *de novo* Patients with Parkinson’s Disease

Jae Jung Lee¹ and Jong Sam Baik²

¹Department of Neurology, Ilsan Paik Hospital, Inje University College of Medicine, Goyang; ²Department of Neurology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea.

**Purpose:** This study aimed to investigate the prevalence of peripheral neuropathy (PNP) and its related serum metabolites in *de novo* patients with Parkinson’s disease (PD). PNP is a type of frequent comorbidity in PD. Although the administration of levodopa has been described as a presumptive risk factor in its development, few studies have explored its effect on unmedicated PD patients.

**Materials and Methods:** This study included 105 drug-naïve *de novo* PD patients. A standardized nerve conduction study (NCS) technique was used to evaluate motor or sensory neuropathy. We analyzed serologic tests including metabolic markers of vitamin B12, homocysteine (Hcy), and uric acid (UA).

**Results:** We found abnormal nerve conduction velocity findings in 24 out of 105 total patients. Among them, 20 patients showed a type of combined motor-sensory, while three were a type of pure sensory and one was a pure motor. Nine patients had carpal tunnel syndrome. PD with PNP group demonstrated higher serum levels of Hcy and UA compared to PD without PNP group.

**Conclusion:** Our data demonstrated a potential role of Hcy and UA on PNP in *de novo* patients with PD. These results suggest the contribution of the inherent metabolic pathway in deterioration of the peripheral nervous system in PD.

**Key Words:** Parkinson’s disease, peripheral neuropathy, homocysteine, uric acid

**INTRODUCTION**

Motor disabilities including tremor, rigidity, and bradykinesia are cardinal symptoms in patients with Parkinson’s disease (PD), but sensory symptoms such as numbness or pain are another frequent complaints throughout the history of the illness.¹² A few studies have demonstrated that peripheral neuropathy (PNP) is more common in PD patients than in the normal population, particularly in patients who are treated with levodopa or intrajejunal levodopa infusion.⁷ Although the exact mechanism of action in dopa-induced PNP is unclear,⁸⁻¹⁰ several metabolic pathways of homocysteine (Hcy), vitamins, or methylmalonic acid (MMA) have been posed to be relevant to the emergence of PNP in PD patients who are treated with levodopa.¹¹ However, to date, little is known about the prevalence of PNP in *de novo* PD patients. Carpal tunnel syndrome (CTS), a type of PNP, was reported at a higher prevalence in PD patients compared to normal controls.¹² Low serum uric acid (UA) is a well-known potential risk factor for multiple neurological disorders, such as Alzheimer’s dementia, Huntington’s disease, amyotrophic lateral sclerosis, and PD.¹³ However, the precise relationship between serum UA and PNP in *de novo* PD patients has not been reported.

To address this uncommon condition, our study investigated the prevalence of PNP in *de novo* patients with PD and its relationship with serum metabolites of Hcy, Vitamin (Vit) B12, and UA.
MATERIALS AND METHODS

We enrolled consecutive patients who met the inclusion criteria for this study in the Parkinson’s clinic over the course of 1 year (2018). The current study obtained written informed consent from all of the participants and was approved by the Institutional Review Board of Sanggye Paik Hospital, Inje University (IRB No. 2018-11-016).

Patients

All patients fulfilled the United Kingdom Brain Bank criteria for clinical diagnosis of PD and were wholly unmedicated. Patients were excluded if they 1) had any history of systemic diseases, such as diabetes, malignancy, chronic alcohol consumption, thyroid disease, rheumatoid arthritis, or chronic renal failure; 2) were being already treated with vitamin B1, B2, B6, or B12, or steroid hormones before or during the study period; or 3) had clinical and electrophysiological evidence of accompanying conditions that could mimic PNP or interfere with its evaluation, such as radiculopathy or marked orthopedic abnormalities. Comprehensive neurological examination, including Hoehn and Yahr stage (H-Y stage) and Unified Parkinson’s Disease Rating Scale part III (UPDRS III), was performed in all patients. Nerve conduction study (NCS) was also administered at the time of PD diagnosis. We analyzed the blood samples obtained in the morning after an overnight fast to evaluate serum metabolite levels.

Nerve conduction study

Using an Excel plus instrument (CADWELL, USA), we measured the sensory nerve conduction velocity (NCV) and motor NCV in air-conditioned room temperature at 23°C to 25°C. To avoid bias, the clinical neurophysiologist was blinded to the patient’s condition. We performed NCS on the upper and lower extremities based on standard laboratory techniques. Antidromic sensory responses from the respective median and ulnar nerves on the right upper extremity were measured. We measured the sural sensory antidromic and peroneal motor nerve conduction on the right lower extremity using standardized techniques and at a fixed distance. No needle examination was performed. We defined the PNPs as including polyneuropathy or neuropathy with NCS abnormalities in either the upper or lower extremity. CTS was also included in the PNP diagnosis.

Statistical analysis

Data are expressed as the mean±SD or number (%). Baseline characteristics of the two groups were compared using the Student’s t-test for continuous variables and χ² test for categorical variables. The Mann-Whitney U test was used to compare the non-normally distributed data, and the Student’s t-test was used to compare normally distributed data. A two-sided p value<0.05 was considered statistically significant. The SAS version 4.2 software (SAS Institute Inc. Cary, NC, USA) was used for statistical analysis.

RESULTS

We included a total of 105 patients with de novo PD in the current study. Baseline characteristics of the study population are shown in Table 1. Twenty-four out of 105 patients (22.8%) had features of PNP on NCV examination in our study. Forty-one out of 105 patients (39%) were female, and the sex ratio was similar between the two groups (42% vs. 38%). The subtype of tremor was observed by 14/24 (58%) in patients with PNP and by 41/81 (51%) in those without PNP. Patients with PNP were older than those without PNP. Otherwise, there was no significant group difference in clinical characteristics including sex ratio, disease duration, PD phenotype, H-Y stage, and UPDRS III score.

In NCV findings of 24 PNP patients, of whom 20 had combined motor and sensory neuropathy in the anterior tibial and sural nerves, three had pure sensory neuropathy, and one patient alone had pure motor neuropathy. We found nine and two cases of CTS and ulnar neuropathy, respectively. Five out of the nine CTS patients clinically demonstrated tremor-dominant type of Parkinsonian features.

We compared the serum metabolites of Vit B12, Hcy, and UA between the two groups (Table 2). The patients with PNP demonstrated significantly higher Hcy and UA levels compared to those without PNP. The Vit B12 level was lower, yet without significance, in the PNP group (Fig. 1).

| Table 1. Baseline Characteristics of the Study Population |
|---------------------------------------------------------|
| **PD with PNP**                                      | **PD without PNP**                     | **p value** |
| (n=24)                                                | (n=81)                                  |
| Age (yr)                                              | 74.1±8.94                               | 67.2±8.94 | 0.002 |
| Female, n (%)                                         | 10 (41.7)                               | 31 (38.3) | 0.765 |
| Disease duration (yr)                                 | 0.9±0.59                                | 1.3±1.33 | 0.225 |
| Subtypes of tremor, n (%)                             | 14 (58.3)                               | 41 (50.6) | 0.506 |
| H-Y stage                                             | 1.5±0.59                                | 1.5±0.65 | 0.975 |
| UPDRS III                                             | 22.6±8.39                               | 22.9±10.52 | 0.884 |
| PD, Parkinson’s disease; PNP, peripheral neuropathy; H-Y, Hoehn and Yahr; UPDRS, Unified Parkinson’s Disease Rating Scale. |

| Table 2. Comparison of Serum Metabolic Markers between PD Patients With and Without PNP |
|-------------------------------------------------|
| **PD with PNP**                                | **PD without PNP**                     | **p value** |
| (n=24)                                         | (n=81)                                  |
| Vitamin B12, pg/mL                              | 647.6±342.67                           | 709.9±349.96 | 0.453 |
| Homocysteine, µmol/L                           | 12.6±3.21                              | 11.0±2.61 | 0.019 |
| Uric acid, mg/dL                                | 5.3±1.21                               | 4.6±1.12 | 0.025 |

PD, Parkinson’s disease; PNP, peripheral neuropathy.
DISCUSSION

In this study, we explored the relationship between PNP and serum metabolites of Vit B12, Hcy, and UA in de novo PD patients. Our results demonstrated that the prevalence of PNP in PD patients without levodopa experience was higher than those in previous studies, and the serum metabolites including Hcy and UA were associated with PNP in de novo PD.

Many patients complain of sensory disturbance as a type of key non-motor symptom in PD. Despite their relentless sensory symptoms, however, a majority of them do not demonstrate abnormal NCV findings, as the mechanism of sensory disturbance in PD is believed to be derived from the central anatomical correlate, such as basal ganglia, instead of the peripheral nervous system. Conversely, some PD patients with abnormal NCS findings used to have no sensory symptoms. Due to this reason, NCS is an important tool for diagnosing the PNP, especially in PD patients. A number of previous reports have discussed the relationship between PNP and PD, and that the metabolites of Vit B12 and Hcy, which are highly implicated with levodopa treatment, play a certain role in its development. However, the study of PNP in de novo PD patients is limited. The prevalence of PNP was 2.4-fold higher in PD patients (0.29%) compared to controls (0.12%) in a previous observational study. Rajabally and Martey showed that 4/33 (12.1%) de novo PD patients, 13/36 (36.1%) levodopa-treated PD patients, and 3/37 (8.1%) controls were diagnosed with co-existing neuropathy. In our study, 24 out of 105 de novo PD patients (22.3%) had features of PNP, which was higher than those of previously reported. A majority of neuropathy (20/24) showed a type of combined motor-sensory neuropathy. A pure sensory type was shown in three patients (0.13%), and a pure motor type was identified in one patient (0.04%) alone. CTS is frequently observed in the older general population. We previously reported that the prevalence of CTS in PD was higher than in normal controls, and concluded that hand tremor in de novo PD patients was not directly related to the development of CTS. We also found that CTS was not related with the tremor subtype of PD.

Serum metabolites of Hcy, MMA, Vit B12, and Vit B6 are well-known risk factors for the emergence of PNP in patients with PD. Hcy has a neurotoxic effect not only in PD, but also in diabetes and in healthy elderly subjects. In light of the acute occurrence of PNP in patients who are treated with levodopa or levodopa/carbidopa intestinal gel infusion, an iatrogenic effect of dopaminergic treatment is highly presumed to be involved. Although the precise mechanism of these metabolites in dopa-treated PD patients is yet to be elucidated, a deficiency of Vit B12 or B6 may cause neuronal damage by elevating the plasma Hcy level and altering Vit B12-dependent RNA methylation. These changes may result in a reduction of both carbohydrate and fat metabolism, and impair the production and repair of axonal protein. Based on this postulation, the dopa-induced PNP may frequently be related to elevated plasma Hcy and Vit B12 deficiency, respectively. The increase in Hcy during oral L-dopa as well as LCIG infusion are related to the consumption of methyl groups by catechol-O-methyltransferase (COMT). For this reason, the inhibitors of COMT can effectively reduce plasma Hcy levels. Another putative mechanism of PNP in unmedicated PD includes neurodegeneration or neurotoxicity direct to the peripheral nervous system. Hcy may cause neurotoxicity by increasing vulnerability to mitochondrial toxins, glutamatergic excitotoxicity, and impairing DNA repair mechanisms by inducing inflammatory reactions. Our result of higher Hcy in the PNP group underpin these previous mechanisms of neurotoxicity in de novo patients with PD. We also observed the serum UA level to be higher in the PD patients with PNP than in those without PNP. Serum UA level may also play an important role in the pathophysiology of neurodegenerative disorders. Unfortunately, the specific role of the UA in the development of PNP in PD has not been fully understood yet. Alternatively, systemic conditions including renal, hepatic, or thyroid function might affect the serum UA and Hcy levels, and further lead to the emergence of PNP in patients with PD. To best minimize such confounding effects, we had already excluded the individuals with abnormal metabolic disorders, such as renal failure, thyroid disease, or liver disease, from the outset of the study enrollment.

The current study had some strengths and limitations. Despite having obtained a large volume of the study population, we evaluated the neuropathy using NCV alone without further

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**Fig. 1.** The distribution of serum (A) vitamin B12, (B) homocysteine, and (C) uric acid in Parkinson’s disease (PD) patients with and without peripheral neuropathy.
assessments, such as a quantitative sensory test or tissue biopsy. This prevented us to identify conclusive subtype of neuropathy and detailed pathological changes. Additionally, we analyzed our data within the de novo PD patients and had no data on healthy controls in the same population. Owing to this reason, we could not directly compare the prevalence of PNP between the de novo PD patients and healthy control groups. We also did not explore the potential alterations in the follow-up NCS test after the introduction of PD medication. Lastly, the bias of aging, a primary risk factor for PNP in PD, cannot be ruled out in this study. Despite these limitations, however, we confirmed the serum level of higher in Hcy and lower in Vit B12, respectively, after PNP in de novo PD patients. These results supported the hypothesis that Hcy and Vit B12 may also play a certain role in the pathogenesis of PNP in de novo PD, not only in the case of levodopa-induced PNP. The UA may be involved in similar contribution as well. Further long-term studies with a larger sample size are warranted to validate our findings.

AUTHOR CONTRIBUTIONS

Conceptualization: Jong Sam Baik. Data curation: Jae Jung Lee and Jong Sam Baik. Formal analysis: Jae Jung Lee. Funding acquisition: Jong Sam Baik. Investigation: Jae Jung Lee. Methodology: Jong Sam Baik. Project administration: Jong Sam Baik. Resources: Jae Jung Lee. Software: Jae Jung Lee. Supervision: Jong Sam Baik. Validation: Jae Jung Lee. Visualization: Jong Sam Baik. Writing—original draft: Jae Jung Lee. Writing—review & editing: Jong Sam Baik. Approval of final manuscript: all authors.

ORCID iDs

Jae Jung Lee https://orcid.org/0000-0001-6799-1564
Jong Sam Baik https://orcid.org/0000-0002-5300-203X

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