Original Article

# Neuropathy in Parkinson's Disease: Risk Determinants and Impact on Quality of Life

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## Abstract

Neuropathy has been described in significantly higher proportion of PD patients than in control subjects. This study ascertains the prevelance of neuropathy and its determinants in PD patients, in particular relation with nutritional status, along with impact of neuropathy on Quality of life. **Methods:** This was a hospital based observational cross-sectional study of PD patients attending the Neurology OPD of a tertiary care hospital. The prevalence and type of neuropathy was determined using the validated MNSI scale. The nutritional status was assessed using MNA score and PDQ-39 was used for assessing quality of life. Patients with and without neuropathy were compared to ascertain risk factors for neuropathy. **Results:** Twenty-four out of 93 PD patients (26%) had neuropathy and 12 (50%) out of them had painful neuropathy. Older patents and those who had longer duration of disease had higher prevalence of neuropathy. In addition there was significant correlation with malnutrition and neuropathy. 79% of patients with neuropathy had abnormal nutritional status. On comparison of patients with painful neuropathy as compared to those without pain, Vitamin B 12 levels were found to be low only in the former group. **Conclusions:** Our study shows that there is significant prevalence of neuropathy in PD patents that affects the quality of life of PD patients. Neuropathy in PD is disease dependent and is precipitated by malnutrition. Hence, neuropathy must be timely diagnosed and effective nutritional management may help to improve the patient's quality of life.

**Keywords:** Malnutrition, neuropathy, Parkinson's disease, quality of life

## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease with a prevalence of 18/100,000/year and usually develops later in life.[1] PD is now better described as a multisystem disorder affecting the peripheral nervous system, gastrointestinal system and autonomic system besides the central nervous system and leads to cardinal motor as well as non-motor symptoms.[2,3]

Among the various non-motor symptoms, neuropathy is one of the important symptom affecting PD patients. Studies from the western countries have shown increased prevalence of neuropathy in PD patients as compared to controls.[4,5] Though various factors have been studied to ascertain their role in the etiology and pathogenesis of neuropathy in PD patients, most studies have shown only conflicting results. Few pathological studies suggest that neuropathy is due to the degenerative process of the nerve fibers while others suggest that it might be related to nutrient factors.[6]

There is growing evidence to show that malnutrition is widely prevalent in PD patients and ensues clinical problems such as negative energy balance, weight loss, falls, bone fracture, and infections.[7] In addition, malnutrition impacts the course of PD disease with cognitive impairment and orthostatic hypotension resulting in increasing disability and mortality.[8] PD-related neuropathy is etiologically multifactorial. It may be related to the disease process itself or levodopa treatment or may be a consequence of malnutrition which is still obscure. There are no studies from the Asian subcontinent correlating the role of nutrition and neuropathy in PD patients. Hence, this study addresses the potential determinants of PD-related neuropathy and its impact on quality of life (QOL).

## Materials and Methods

This was a single center observational cross-sectional study conducted in the outpatient neurology department of a tertiary care hospital of north India. The Institutional Ethics committee of the institute approved the study.

### Study group

Patients with diagnosis of Idiopathic PD (according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria) who visited the outpatient department (OPD) for their regular follow-ups were included in the study after obtaining

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their consent. Patients with co-morbidities such as diabetes mellitus, alcohol abuse, malabsorption syndromes, thyroid disease and those on any vitamin supplementation were excluded. Patients with diagnosis of secondary Parkinsonism were also excluded from the study.

### Data collection

A predesigned performa was used to record patients' demographics including age, gender, height, weight, body mass index (BMI), age at onset, and duration of disease. Modified Hoehn & Yahr (H&Y) score was assigned to each patient for staging of the disease. The details of each patient's current treatment regimen were recorded including details of Levodopa and dopaminergic agonist dosage. Levodopa equivalent dose (LED) was also calculated for each patient. Serum B12 levels were obtained for all patients on their outpatient visit.

#### *Neuropathy stratification method*

Michigan Neuropathy Screening Instrument (MNSI) questionnaire was used to assess the presence of distal symmetrical neuropathy. This is a validated questionnaire comprising of two parts. The first part has15-items with each question being highly specific to confirm neuropathy and is verbally administered to the patient. The second part involves physical examination of lower limbs of the patient for any ulcers, sensory examination (monofilament test), vibration sense, and ankle reflex for confirming the diagnosis of neuropathy. The MNSI score has good reliability in predicting clinical neuropathy if the score of the second part is >2.5. Further the neuropathy was subtyped as painful or painless neuropathy based on the positive response to the item 2 (*Do you ever have any burning pain in your legs and/or feet*?), item 3 (*Are your feet too sensitive to touch*?), and item 6 (*Does it hurt when the bed covers touch your skin*?) of the first part of MNSI questionnaire.

#### *Mini nutritional assessment (MNA)*

This questionnaire was used to assess nutritional status of PD patients, which comprises of 18 questions with a total score of 30 points. The nutritional status was further quantified as "*normal nutritional status*", "*at risk for malnourishment*" or "*malnourished*" based on the score ≥24; between 17 and 23.5 or <17, respectively. Those with a score <24 were considered as having abnormal nutritional status.

#### *Quality of life (PDQ-39)*

QOL was evaluated by using Parkinson's disease questionnaire-39 (PDQ 39), a self-rated measure of health status and health-related QoL. PDQ39 comprises of 39 questions which assess 8 different dimensions of life such as mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and pain.

### Statistical analysis

Data were described in terms of range; mean ± standard deviation (± SD), frequencies (number of cases), and relative frequencies (percentages) as appropriate. To determine whether the data were normally distributed, a Kolmogorov–Smirnov test was used. Comparison of quantitative variables between the study groups was done using Student *t*-test and Mann Whitney *U* test for independent samples for parametric and non-parametric data, respectively. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency is < 5. A probability value (*P* value) <0.05 were considered statistically significant. All statistical calculations were done using Statistical Package for the Social Science (SPSS) 21 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

## Results

### Study population

We screened 118 PD patients who visited the neurology OPD during the study period, out of which 93 patients were included in the study. Of these 20 patients were excluded from the study as 14 had coexistent diabetes mellitus, 3 patients had thyroid disease, 4 had history of alcohol abuse, and the remaining 4 patients were on vitamin supplementation. Hence, 93 consenting patients with PD (68 males and 25 females) were recruited in the study. Mean age of PD patients was 61.72 ± 9.6 years. Mean duration of disease was 4.92 ± 3.45 years with severity on H&Y scale ranging 1–4, with median of 3. In our cohort, 27 (29%) patients had normal nutritional status, 58 (62%) were at risk of malnutrition, while 8 (9%) were malnourished.

### Status of neuropathy

We diagnosed neuropathy in 24 (25.8%) out of the 93 PD patients using MNSI Questionnaire. Among 24 patients with neuropathy, 50% reported painful neuropathy as ascertained by items 2, 3, and 6 of the neuropathy questionnaire. Further classifying the type of pain, six reported burning pain, four had hyperalgesia, and two patients had allodynia as a manifestation

**Table 1: Demographic, clinical characteristic, and determinants of neuropathy in patients with PD**

| Demographic and clinical characteristics | PD without neuropathy *n*-69 (mean±SD; %) | PD with neuropathy *n*-24 (mean±SD; %) | *P* |
|---|---|---|---|
| Age | 64.04±8.74 | 68.75±7.70 | 0.011 |
| Gender | | | |
| Male | 18 (26) | 7 (29) | 0.769 |
| Female | 51 (74) | 17 (71) | |
| Duration | 4.11±2.53 | 6.63±4.07 | 0.005 |
| H&Y | | | |
| Stage 1 | 15 (22) | 1 (4) | 0.199 |
| Stage 2 | 40 (58) | 16 (67) | |
| Stage 3 | 13 (19) | 7 (29) | |
| Stage 4 | 1 (1) | 0 | |
| UPDRS | 63.78±15.61 | 68.50±10.62 | 0.093 |
| LEED | 446.94±231.98 | 495.69±254.04 | 0.396 |
| B12 (pg) | 457.14±253.31 | 320.38±239.45 | 0.295 |
| MNA | 22.01±2.95 | 19.33±2.88 | 0.023 |
| Nutritional status | | | |
| PDQ- 39 | 21.74±10.71 | 30.16±11.66 | 0.002 |

of painful neuropathy. Clinical and disease characteristics of PD patients with or without peripheral neuropathy are summarized in Table 1. To evaluate the risk factors for peripheral neuropathy, we compared the patients of PD with peripheral neuropathy with those who did not have peripheral neuropathy. These two groups were significantly different with regard to age ($P = 0.01$) and duration of disease ($P = 0.005$). PD patients who were older (68.75 ± 7.70 years) and had longer duration of disease (6.63 ± 4.07 years) reported neuropathy more frequently as compared to younger PD patients with shorter disease duration.

In addition, poor nutritional status was also seen to be significantly associated with the presence of neuropathy. Out of the 24 patients with neuropathy, 79% had abnormal nutritional status. The mean MNA score in PD patients with neuropathy and without neuropathy was 19.33 ± 2.88 and 22.01 ± 2.95, respectively, and this difference was statistically significant ($P = 0.23$). The odds ratio of association of malnutrition with neuropathy in PD patients is 1.77 (95% CI; 0.58–5.38). However, in our study we did not find any statistically significant difference of gender, Levodopa equivalent dose (LED), and severity of disease in patients with regard to presence or absence of neuropathy.

Also PD patients with or without neuropathy did not differ in their B12 levels. However, PD patients with painful neuropathy when compared with non-painful neuropathy patients for baseline characteristics had significant difference only in B12 levels. The PD patients with painful neuropathy had significantly lower mean B12 levels that were 172.60 ± 29.64 ($P = 0.024$) as compared to the PD patients with non-painful neuropathy in whom B12 levels were 566.67 ± 230.94. These two groups did not differ significantly regarding age, gender, duration, and severity of disease, LEED, or MNA scores.

### Impact of neuropathy on QOL

The presence of neuropathy was significant and inversely associated with QOL ($P = 0.02$). Among the different dimensions of life, mobility ($P = 0.010$), activities of daily living ($P = 0.001$), cognition ($P = 0.037$), and bodily discomfort ($P = 0.011$) were selectively more severely affected by the presence of neuropathy [Table 2]. Though, the presence of pain with neuropathy did not have any additional impact on QOL of PD patients with painful neuropathy versus those without painful neuropathy [Figure 1]. Summary of significant findings have been depicted in Figure 2.

**Table 2: Comparison of QOL using PDQ-39 in PD patients with and without neuropathy**

| PDQ-39 scales with different domains | PD- without neuropathy *n*-69 (mean±SD) | PD with neuropathy *n*-24 (mean±SD) | *P* |
|---|---|---|---|
| PDQ-39 | 21.74±10.71 | 30.16±11.66 | 0.002 |
| Mobility | 31.99±24.89 | 42.92±25.21 | 0.010 |
| Activities of daily living | 33.02±25.96 | 55.54±24.91 | 0.001 |
| Emotional well-being | 24.75±19.81 | 27.76±20.00 | 0.224 |
| Stigma | 16.99±29.79 | 31.77±31.44 | 0.405 |
| Social support | 3.25±9.38 | 3.47±6.50 | 0.078 |
| Cognition | 16.88±12.66 | 25.55±18.86 | 0.037 |
| Communication | 21.54±22.82 | 26.34±19.65 | 0.487 |
| Bodily discomfort | 23.52±18.83 | 36.10±22.55 | 0.011 |

## Discussion

Our results show that peripheral neuropathy is present in 26% of PD patients with 50% of them having painful type of neuropathy. Increasing age, disease duration, and malnutrition were the significant factors associated with neuropathy in PD patients. In addition, we observed significantly low levels of vitamin B12 in patients who had painful neuropathy. Presence of neuropathy certainly affected certain domains of QOL in PD patients.

Previous studies on the presence of neuropathy in PD showed that it is more prevalent in PD patients than controls.[4,5] Prevalence of neuropathy was 0.3% in the naïve patients of PD making them 2.4 fold at risk as compared to control population. In a study by Rajabally *et al*. from the United Kingdom stated incidence of peripheral neuropathy to be as high as 37% in patients of PD but our incidence is slightly less than reported by them.[5] This difference may be due to the inclusion criteria and methods used for diagnosing neuropathy. Both are questionnaire-based studies and can have recall bias. But diagnosis of peripheral neuropaty (PN) by Rajabally *et al*. was supplemented by electrophysiological assessment also which could be the cause for higher incidence.[5] These numbers are, however, markedly high, as compared to 0.3% incidence of PN reported in drug naïve patients, meaning early stage of the disease or initial visits in OPD while, mean duration of disease in our patients was 4.92 ± 3.45 years with severity on H&Y scale ranging 1–4, with median of 3.

There has been varying evidence in literature about the determinants of risk factors for neuropathy. Among the various factors studied, B12 deficiency secondary to levodopa therapy

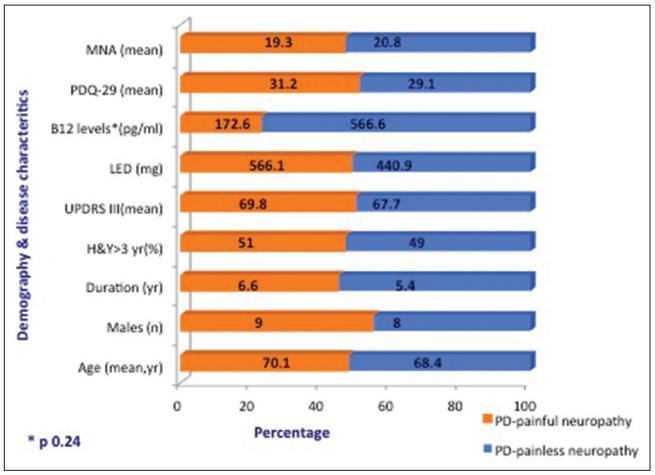


**Figure 1:** Analysis of demographic and clinical risk factors associated with painful and non-painful neuropathy in PD patients

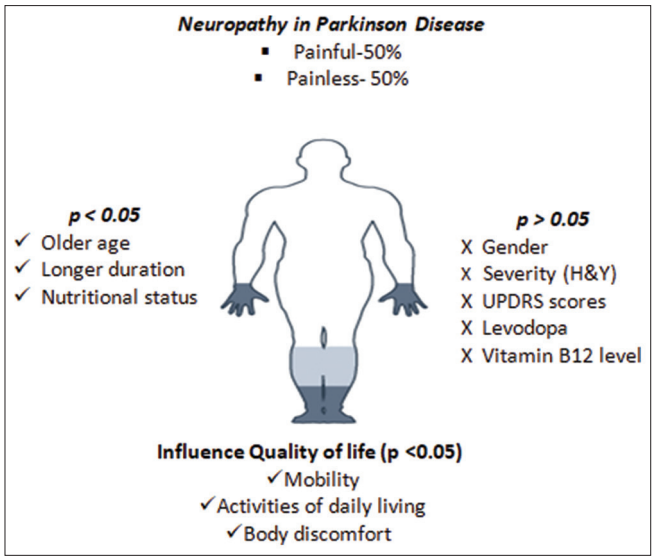


**Figure 2:** Determinants of peripheral neuropathy analyzed along with significant findings among 93 patients of PD

has been attributed to be the main cause for neuropathy in PD patients.[4] While others suggest that the presence of genetic mutations is the cause of PD-related neuropathy.[9] To the best of our knowledge, this is the first study to access the corelation of nutritional status assessed by MNA scale with peripheral neuropathy and its impact on QOL of PD patients. Our findings favor old age and increasing duration of disease as the most significant risk factors for the occurrence of neuropathy in PD. This supports the fact that there may be a link between peripheral and central neuronal degenerative process linked with PD. Literature also supports strong association of neuropathy in PD patients who had *Parkin gene*mutation, which results in peripheral degeneration of the epidermal nerve fibers.[10]

Adewusi *et al*.[11] reported that duration of disease and years on levodopa were significantly higher in PD patients who had neuropathy. This highlights that peripheral neuropathy is a late manifestation noted in the course of disease and is in coherence with our results.

Also, Adewusi *et al*. did not find any association of cumulative levodopa with neuropathy similar to our observation.[11] Previous data has shown the presence of neuropathy in naïve PD patients, hence neuropathy was seen in patients who had not received any dose of levodopa. Hence, it can be safely concluded that levodopa is not the sole cause of PD-related neuropathy. Its role in peripheral neuropathy is unclear and needs to be explored in further studies.

There are conflicting results regarding association of B12 levels with presence of neuropathy in PD patients. Studies showed that vitamin B12 deficiency was a common cause of neuropathy while a study undertaken in an Indian cohort of PD patients showed no difference in the vitamin levels in patients with or without neuropathy.[12] Though, in our cohort, B12 levels were found to be low only in patients who had painful neuropathy.

Malnutrition is a term used for both macro- and micronutrient deficiency. If these nutrients are not available in sufficient amounts, it may result in a spectrum of neurological disorders with peripheral neuropathy being one of them as nutrients like copper, selenium, vitamin A, and thiamine are essential cofactors for maintaining integrity of nerve cell.[13] Deficiencies of these nutrients especially in PD patients can be in the context of malnutrition. Previous study done by the authors on nutritional status in PD found that 45.3% of PD patients are at a risk of malnourishment and 12% PD patients suffered from malnutrition, and there was a significant correlation of gastrointestinal disturbances like constipation and dysphagia with the presence of malnutrition.[14] The reasons for malnutrition in PD patients are multifactorial and may even be a part of spectrum of non-motor symptoms of PD. This plausible cause-effect co-relation of malabsorption which is a significant co-morbid condition in PD and abnormalities in nutrient levels leading to peripheral neuropathy needs to be evaluated in future studies with biochemical evidence.

The present study also explored the impact of neuropathy on QOL in patients with PD (after adjusting for the other factors). Our analysis revealed that peripheral neuropathy had an independent negative impact on certain domains of life. Physical functioning and mental domains were more severely affected than others. Hence, factors causing peripheral neuropathy which in turn contributing to poor QOL should be identified in PD cohort. Also, measures such as physical rehabilitation, pharmacotherapy, and nutritional supplementation should be provided timely to appropriate PD patients to improve not only their functional outcome but also QOL.

Motor functioning in PD reduces with increasing age and duration of disease, hence affecting activities of daily living and mobility. In addition to this, neuropathy may also impair motor functioning, making it difficult for these patients to maintain their nutritional needs. This may be the reason for this group of patients to have high rates of nutritional abnormalities. Further, an impairment of cognition and bodily discomfort may further add to their nutritional needs to be unmet.

Our study has some limitations that should be considered. First, we used MNSI 15-item questionnaire and lower extremity examination rather than electrophysiological assessment for diagnosis of neuropathy. But each of these 15 items of MSNI is known to be very specific individually as the absence of correspondent symptoms can exclude a diagnosis of peripheral neuropathy.[15,16] In addition, this structured questionnaire aids in further subgrouping neuropathy as painful or not. Second, we used MNA scoring for accessing the nutritional indicators rather than biochemical parameters (albumin levels and hemoglobin levels). MNA is an innovative, comprehensive and multidimensional tool containing range of questions, and anthropometric parameters, which were used to assess the nutritional status of patients. Lastly, we did not include a control group for comparison.

Despite these limitations, our study is the first to correlate nutritional status of PD patients with neuropathy in Indian population by using reliable and validated questionnaires.

## Conclusion

Our study shows that there is significant prevalence of neuropathy in PD that affects the QOL of PD patients in both, motor and non-motor aspects. The presence of neuropathy is correlated with the increasing age and duration of disease, and inversely with the nutritional status of PD patients. Thus, neuropathy must be timely diagnosed and effective nutritional management may help improve the patient's QOL as well as functional status.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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