RESEARCH ARTICLE

Neuropathy and Levodopa in Parkinson's Disease: Evidence From a Multicenter Study

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ABSTRACT: The objectives of this study were to evaluate the risk of neuropathy in patients with Parkinson's disease (PD) and to evaluate the role of levodopa exposure as a potential risk factor. A multicenter study of 330 patients with PD and 137 healthy controls with a comparable age distribution was performed. With respect to levodopa exposure, 144 patients had long exposure ($\geq$3 years) to levodopa (LELD), 103 patients had short exposure (<3 years) to levodopa (SELD), and 83 patients had no exposure to levodopa (NOLD). Nerve function was evaluated using the reduced total neuropathy score. Right sural sensory antidromic and peroneal motor nerve conduction studies were performed by neurophysiologists who were blinded to the existence of neuropathy clinical features or PD treatment. Overall, 19.40% of patients in the LELD group, 6.80% in the SELD group, 4.82% in the NOLD group, and 8.76% in the control group were diagnosed with neuropathy (axonal, predominantly sensory). Multivariate logistic analysis indicated that the risk of neuropathy was not influenced by disease duration, severity, or sex. The risk of neuropathy increased by approximately 8% for each year of age ($P < 0.001$; odds ratio [OR], 1.08; 95% confidence interval [CI], 1.037-1.128). The risk of neuropathy was 2.38 higher in the LELD group than in the control group ($P = 0.022$; OR, 2.38; 95% CI, 1.130-5.014). In a comparison between patients with and without neuropathy (Student's t test), the levodopa dose was higher ($P < 0.0001$), serum vitamin B12 levels were lower ($P = 0.0102$), and homocysteine levels were higher ($P < 0.001$) in the patients with neuropathy. Our results demonstrate that the duration of exposure to levodopa, along with age, is the main risk factor for the development of neuropathy. Screening for homocysteine and vitamin B12 levels and clinical-neurophysiological monitoring for neuropathy may be advisable in patients with PD who are receiving treatment with levodopa. © 2013 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; peripheral neuropathy

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Parkinson's disease (PD) is a common neurodegenerative disorder that can cause significant disability and decreases quality of life. The cardinal physical signs of the disease are distal resting tremor, rigidity, bradykinesia, and asymmetric onset. However, mostly in the later stages of the disease, postural instability, muscular cramps, and numbness—more prominent in feet and distal legs—also can occur. These latter symptoms also are distinctive of a distal, predominantly sensory neuropathy. This overlap between different clinical entities may explain why for many years neurologists might have overlooked the concurrence of peripheral involvement as a possible additional cause of motor performance and quality-of-life worsening in patients with PD. Only in recent years have some studies systematically assessed the presence of neuropathy in PD populations,[1–3] suggesting that patients with idiopathic PD frequently may present clinical and/or neurophysiological features of polyneuropathy.

However, some important questions remain open. In particular, mainly due to some methodological limitations, like studies that analyzed only case series,[1] single-center studies,[2,3] and studies that lacked or included only small groups of patients with PD who had no levodopa (L-dopa) exposure in the study design,[1–3] previous studies were unable to reach a definitive conclusion on the causes responsible for the neuropathy. To ascertain the risk factors for neuropathy in idiopathic PD, and particularly whether L-dopa plays a crucial, causative role, we carried out a multicenter clinical/neurophysiological study in a large sample of patients with PD and age-matched controls, stratifying our PD population on the basis of the duration of L-dopa exposure.

Patients and Methods

Between January and November 2011, we conducted a cross-sectional study involving six Italian tertiary referral centers for PD (Cagliari, Genoa, Naples, Pisa, Turin, and Viareggio) by enrolling consecutive patients who met inclusion criteria for the study. This study received approval from the ethical committees of each center. A written informed consent form was obtained from each patient.

Patients

All patients fulfilled United Kingdom Brain Bank criteria for the clinical diagnosis of PD, and the diagnosis was determined by movement disorders specialists. We excluded patients from this study who had a history of other systemic illnesses, such as chronic infectious diseases, diabetes, or other metabolic, endocrine, or autoimmune illnesses; cancer; chronic alcohol consumption; toxic exposure, and any family history of neuropathy. The daily dose and duration of L-dopa

and dopamine agonists were determined for each patient by a retrospective chart review. We defined the daily L-dopa dose as the average daily dosage of L-dopa in the last 6 months. With respect to L-dopa exposure, patients were subdivided into those with exposure for more than three years (long exposure to L-dopa [LELD]), exposure for less than three years (short exposure to L-dopa [SELD]), or no exposure (no L-dopa [NOLD]). The criterion for defining SELD as a period no longer than three years was arbitrary; however, it was driven by the fact that, after three or four years of L-dopa, up to 50% of PD patients can develop dyskinesias and motor fluctuations[4]; this effect is the clinical reflection of a breakdown of a neuronal homeostasis in the central nervous system. Moreover, although the objective of our research was to explore the peripheral nervous system, we decided to tighten the window of L-dopa exposure to this period. Assessment using the motor subscale (part III) from the Unified Parkinson's Disease Rating Scale (UPDRS III) and a complete neurological examination were carried out in all patients. No patients were taking any vitamin supplementation.

Controls were mainly recruited from the familial/social network of the patients and had no history of neurodegenerative disease or other illness that putatively affects peripheral nerves. Age distribution for the control group was comparable to that for the PD group.

Procedures

Nerve function was evaluated using a sensitive, validated neuropathy composite score, the reduced version of the total neuropathy score (TNSr), which is the version previously validated by Cornblath et al[5] and modified by Cavaletti et al[6] (ie, evaluation of sensory symptoms, pin sensibility, vibration sensibility, strength, and deep tendon reflex, without the quantitative determination of vibration threshold but with the neurophysiological investigation of sensory sural and motor peroneal peripheral nerves). For each patient and control participant, a detailed neurological history (with particular reference to the presence of signs of peripheral nerve damage) was drawn up.

As required for TNS design, the presence of sensory, motor, or autonomic symptoms was first assessed by interviewing the patients. The neurological examination was based on the standard evaluation of strength, deep tendon reflexes, and examination of pin sensibility using a sterile disposable needle; and disturbance of vibration sensibility was demonstrated by decreased perception of the 128-Hz diapason vibration, as described by Cavaletti et al.[6]

Nerve conduction studies were performed using standard laboratory techniques. Right sural sensory antidromic and peroneal motor nerve conduction was

studied using standardized techniques and fixed distances. The temperature was maintained at >32°C. To avoid any bias, the clinical neurophysiologist was blinded to the participant's condition (ie, exposure to L-dopa or drug dosages of PD patients, existence of clinical features of neuropathy).

To calculate the TNSr, the amplitude of the antidromic sensory potential in one sural nerve and the compound muscle action potential (CMAP) in the ipsilateral common peroneal nerve were used. The neurophysiological normal reference values necessary for TNS calculation were previously determined in each neurological department in age-matched individuals. According to the results from the clinical and neurophysiological examinations, the TNSr score was calculated as previously described.[5] For each item, the possible score ranged from 0 (normal) to 4 (worst possible results), so that the score ranged from 0 to 28.

According to previously published criteria,[7] only patients who presented a combination of neuropathic symptoms or signs with at least an abnormal parameter in one of the explored nerves were considered as patients with neuropathy. We determined serum vitamin B12 and homocysteine (Hcy) levels for all patients involved in the study. Fasting blood tests were carried out 12 hours after the last dose of L-dopa. For those with neuropathy, we performed further blood investigations, including complete blood count, urea, creatinine, liver enzymes, liver function tests, glucose and hemoglobin A1C (HbA1C), electrolytes, thyroid function (free tri-iodothyronine, free tetraiodothyronine, thyroid-stimulating hormone), erythrocyte sedimentation rate, polymerase chain reaction, antinuclear antibody, extracted nuclear antibody testing, rheumatoid factor, and serum protein electrophoresis.

Statistical Analysis

An initial multivariate logistic analysis was used to demonstrate the possible effects on neuropathy occurrence of L-dopa exposure, age, sex, disease duration, disease severity, and blood levels of vitamin B12 and Hcy. The analysis was carried out considering neuropathy as a dependent variable and considering duration of L-dopa exposure, global UPDRS III score (categorical variable), sex, age (continuous variable), and their second-order interactions as independent variables. Disease duration and levels of vitamin B12 and Hcy (independent continuous variables) were considered without interactions.

On the basis of the results, a second logistic analysis was performed that included only patients with PD to demonstrate the possible independent effects of age on neuropathy (considered as a confounding variable) and L-dopa exposure (LELD vs SELD and NOLD). A multivariate logistic analysis was performed using a backward stepwise procedure based on eliminating the least significant interaction and independent variables at each step. The Student t test for the comparison of two means was used to evaluate differences in serum vitamin B12 and Hcy levels, TNSr score, sensory action potential amplitude of the sural nerve, CMAP amplitude of the peroneal nerve, and L-dopa daily dose between patients with and without neuropathy.

The eventual difference in the pull test score (UPDRS III, sub-item 30) between patients with and without neuropathy was evaluated with the z test for difference between two proportions. A P value < 0.05 was considered significant. Data from the survey were analyzed using the Statistical Package for the Social Sciences (version 19; SPSS Inc., Chicago, IL, USA).

Results

Between January and November 2011, 472 participants (335 patients with PD and 137 age-matched controls) were consecutively screened. Four patients were subsequently excluded because hematological findings disclosed previously unrecognized diabetes (high glucose or HbA1C levels in three patients) or monoclonal gammopathy (one patient); another patient was excluded because as he was diagnosed with cancer after the screening visit.

Of the patients with PD who were finally included, 144 patients (56 women) had L-dopa exposure longer than 3 years (LELD; mean age, 69.1 years; mean illness duration, 9.9 years; mean UPDRS III score, 24.1); 103 patients (38 women) had L-dopa exposure shorter than 3 years (SELD; mean age, 67.6 years; mean illness duration, 3.8 years; mean UPDRS III score, 18.2); and 83 patients (34 women) had no exposure to L-dopa (NOLD; mean age, 62.0 years; mean illness duration, 3.0 years; mean UPDRS III score, 15.7). There were 137 controls (70 women; mean age, 68.0 years).

Twenty-eight of 144 patients (19.40%) with LELD, seven of 103 patients (6.80%) with SELD, four of 83 patients (4.82%) with NOLD, and 12 of 137 age-matched controls (8.76%) were diagnosed with neuropathy (see Tables 1 and 2). The TNSr score was significantly higher in patients with neuropathy than in those without neuropathy (difference in absolute value, 9.8; $P < 0.0001$; 95% confidence interval [CI], 8.9–10.7); the amplitude of the sensory potential of the sural nerve (RV) was significantly lower in patients with neuropathy than in those without neuropathy (difference in absolute value, 9.0; $P < 0.0001$; 95% CI, 8.22-9.88). Also, the CMAP of the common peroneal nerve (mV) was significantly lower in patients with neuropathy than in those without neuropathy (difference in absolute value, 2.6; $P < 0.0001$; 95% CI, 1.96-3.14). The clinical and electrophysiological features of the neuropathic patients were consistent with an axonal, predominantly sensory neuropathy.

TABLE 1. Clinical and demographic characteristics of subgroups in the study population

Characteristic	No. of patients	Mean age, y	Mean duration of illness, y	Mean UPDRS-III score
LELD				
Women, n = 56				
Without neuropathy	46	67.4	9.8	24.3
With neuropathy	10	71.1	12.2	29.9
Men, n = 88				
Without neuropathy	70	69.0	9.9	22.0
With neuropathy	18	72.9	8.7	28.2
SELD				
Women, n = 38				
Without neuropathy	37	66.6	3.4	19.6
With neuropathy	1	74.0	1.0	15.0
Men, n = 65				
Without neuropathy	59	67.8	4.2	17.0
With neuropathy	6	69.7	3.9	20.0
NOLD				
Women, n = 34				
Without neuropathy	33	62.1	2.7	16.6
With neuropathy	1	70.0	1.0	8.0
Men, n = 49				
Without neuropathy	46	61.2	3.2	14.7
With neuropathy	3	69.7	1.0	15.0
Controls				
Women, n = 70				
Without neuropathy	65	66.8		
With neuropathy	5	73.6		
Men, n = 67				
Without neuropathy	60	67.9		
With neuropathy	7	75.4		

UPDRS-III, Unified Parkinson's Disease Rating Scale, motor part; LELD, long exposure to L-dopa (>3 years); SELD, short exposure to L-dopa (≤3 years); NOLD, no exposure to L-dopa.

The first multivariate logistic analysis demonstrated that all interactions were not statistically significant; therefore, they were eliminated from the model. Moreover, the analysis indicated that the risk of neuropathy was not influenced by disease duration (P = 0.91; odds ratio [OR], 1.01), disease severity assessed by the UPDRS III total score (P = 0.20; OR, 1.02), sex (P = 0.25; OR, 1.64), serum vitamin B12 level (P = 0.26; OR, 0.99), or serum Hcy level (P = 0.59; OR, 1.01). Consequently, these variables were eliminated from the model. In the end, the risk of neuropathy increased by 8% for each year of age (P < 0.001; OR, 1.08; 95% confidence interval [CI], 1.037-1.128). Moreover, the risk of neuropathy was 2.38 higher in individuals who had LELD than in healthy individuals (P = 0.022; OR, 2.38; 95% CI, 1.130-5.014). The logistic regression model (Table 3) clearly indicated that age and LELD were independently associated with neuropathy.

TABLE 2. Prevalence of neuropathy in the four patient groups

	No. of patients			
Variable	Without neuropathy	With neuropathy	Total	Prevalence of neuropathy, %
NOLD	79	4	83	4.82
LELD	116	28	144	19.40
SELD	96	7	103	6.80
Controls	125	12	137	8.76
Total	416	51	467	10.92

NOLD, no exposure to L-dopa; LELD, long exposure to L-dopa (>3 years); SELD, short exposure to L-dopa (≤3 years).

TABLE 3. First multivariate logistic regression: Effect of age and L-dopa exposure in patients (no exposure, short exposure, and long exposure to L-dopa) versus controls on neuropathy

Variable	P	OR	95% CI
Age (quantitative variable)	0.00028	1.08	1.037-1.128
NOLD vs controls	0.7255	0.81	0.243-2.678
SELD vs controls	0.5937	0.77	0.286-2.046
LELD vs controls	0.0225	2.38	1.130-5.014

OR, odds ratio; CI, confidence interval; NOLD, no exposure to L-dopa; SELD, short exposure to L-dopa (≤3 years); LELD, long exposure to L-dopa (>3 years).

TABLE 4. Second multivariate logistic regression (considering only patients with Parkinson's disease): Effect of age and long exposure to L-dopa versus short exposure and no exposure to L-dopa

Variable	P	OR	95% CI
Age (quantitative variable)	0.0055	1.07	1.02-1.130
LELD vs SELD and NOLD	0.0035	3.08	1.45-6.56

OR, odds ratio; CI, confidence interval; LELD, long exposure to L-dopa (>3 years); SELD, short exposure to L-dopa (≤3 years); NOLD, no exposure to L-dopa.

The second multivariate logistic analysis (Table 4) unambiguously showed that age and LELD were independently associated with neuropathy. Namely, the risk of neuropathy increased by 7% for each year of age ($P = 0.0055$; OR, 1.07; 95% CI, 1.02-1.12). The risk of neuropathy was 3.083 higher in individuals who had LELD than in individuals who had short exposure and no exposure to L-dopa ($P = 0.0035$; OR, 3.08; 95% CI, 1.45-6.56).

The Student t test indicated that L-dopa dose distribution was significantly higher in patients with neuropathy than in those (LELD and SELD) without neuropathy (difference in absolute value, 404.9; $P < 0.0001$; 95% CI, 321.5–488.3) (Fig. 1).

The results showed that, among patients with PD who were receiving L-dopa (LELD and SELD) and had neuropathy, 22 of 35 had a pull test score ≥2 (UPDRS III, sub-item 30); whereas, among those without neuropathy, only 30 of 212 had a pull test score ≥2, equal to 14%. This difference was significant (z test; $P < 0.0001$).
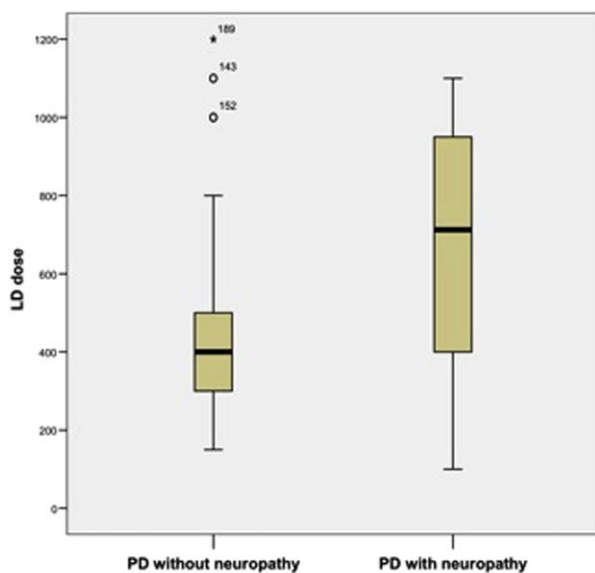
Serum vitamin B12 levels were significantly lower in patients with neuropathy than in those without neuropathy (difference in absolute value, 58.3; $P = 0.0008$; 95% CI, 24.1–92.4) (Fig. 2). Serum Hcy levels were significantly higher in patients with neuropathy than in those without neuropathy (difference in absolute value, 4.2; $P = 0.0001$; 95% CI, 2.03–6.36) (Fig. 3). As stated in the study protocol for the patients with PD who had neuropathy, an additional, extensive hematological investigation was performed, and the results for all neuropathic patients were within normal values.

Discussion

In recent years, some studies have reported an increased prevalence of neuropathy in patients with PD.[1–3] However, those studies shared an important limitation: they only included patients with PD who were exposed to L-dopa. For this reason, although they hypothesized that prolonged L-dopa use directly or indirectly leads to neuropathy, they could not exclude the possibility that other factors, including PD "alone," might cause peripheral impairment.[8] With this unanswered issue in mind, to ascertain whether L-dopa plays a crucial causative role in neuropathy, we choose to stratify our large PD population according to the duration of L-dopa exposure. Moreover, a group of L-dopa-naive PD patients also was studied along with a group of healthy controls.

Our findings provide clear evidence that the duration of L-dopa exposure, but not disease duration or disease severity, is strongly associated with the presence of neuropathy in patients with PD, thus supporting the role of L-dopa as a main risk factor. In
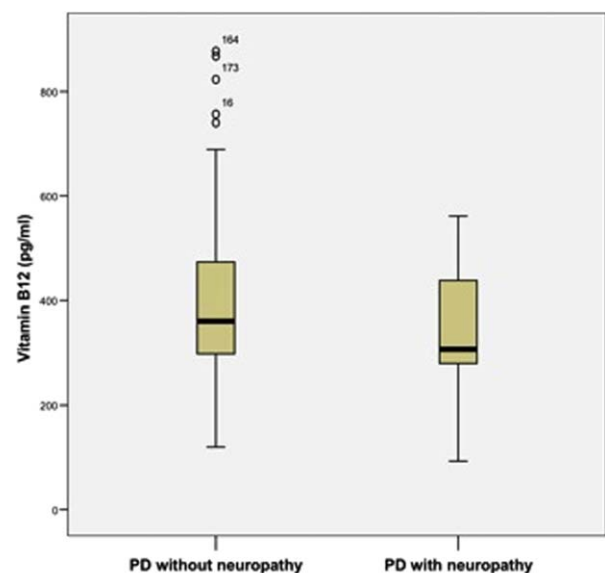

FIG. 1. The distribution of L-dopa (LD) doses (mg/day) in patients who had Parkinson's disease (PD) with and without neuropathy.

FIG. 2. The distribution of serum vitamin B12 levels in patients who had Parkinson's disease (PD) with and without neuropathy.
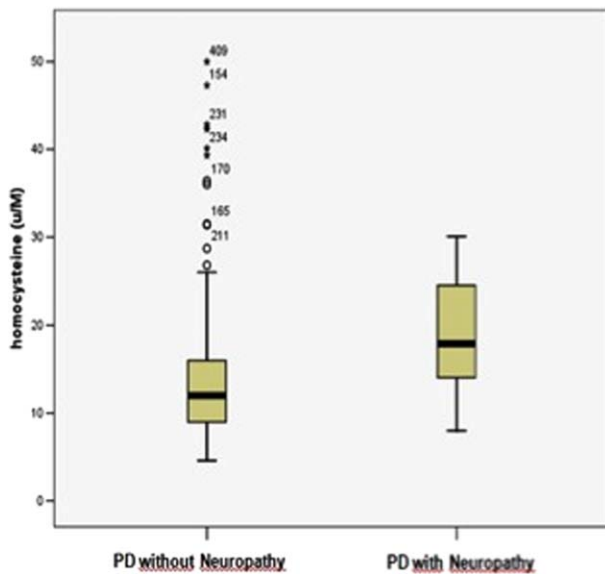
FIG. 3. The distribution of homocysteine levels in patients who had Parkinson's disease (PD) with and without neuropathy.

addition, a positive relationship between the L-dopa daily dose and the presence of neuropathy has been suggested; that is, the longer the duration of L-dopa treatment and, presumably, the higher the L-dopa dose, the greater the risk of neuropathy.

The positive association of neuropathy with both vitamin B12 deficiency and increased Hcy levels observed in our study replicates on a larger scale the data previously published.[1–3,9,10] In particular, our findings are confirmatory of the data originally described by Rajabally and Martey, who reported for the first time a positive relationship between neuropathy and low vitamin B12 levels,[3] as well as recent data regarding a strong association between neuropathy and increased Hcy levels.[1,2]

The increase in Hcy during oral L-dopa as well as duodopa intestinal infusion[11–14] are related to the consumption of methyl groups by COMT; vitamin B12, vitamin B6, and folate are needed cofactors for Hcy metabolism. Vitamin B12 deficiency, which recently was identified as a potential cause of reversible peripheral neuropathy in the elderly,[15,16] reportedly is inversely associated with L-dopa dose in patients who have PD and neuropathy. In most cases, as observed in our study, vitamin B12 levels were significantly lower than those observed in healthy controls, yet they were not always absolutely deficient. This suggests that the neuropathic changes could be related to the exposure to toxic metabolites (Hcy, methylmalonic acid [MMA]) resulting from a combination of high L-dopa concentration and cobalamine functional insufficiency, rather than vitamin B12 deficiency per se.

The increased L-dopa-related Hcy levels and their direct association with the risk of neuropathy observed

in our cohort confirm the potential toxic effects of this metabolite on peripheral nerves. Unfortunately, as a limitation of our study, we could not assess the MMA levels in our patients. Hcy can cause neurotoxicity through several mechanisms, by increasing vulnerability to mitochondrial toxins and rising free radicals, by inducing inflammatory reactions, and also by impairing DNA repair mechanisms.[17–19] L-Dopa-associated, increased Hcy levels reportedly were associated with signs of sural axonal neurodegeneration in an electrophysiological study of patients with PD and healthy controls.[20] The role of high levels of Hcy in inducing peripheral nerve damage has been confirmed in diabetic peripheral neuropathy,[21] in patients with 5,10-methylenetetrahydrofolate reductase deficiency,[22] and in a recent longitudinal clinical and electrophysiological study conducted on a large group of elderly individuals.[23] The evidence that only a proportion of PD patients on L-dopa therapy develop neuropathy could be due to a genetic susceptibility, for example involving methyltetrahydrofolate reductase, for which the potential risk might be related to the possibility of having Hcy elevation with L-dopa therapy.[1]

Because the inhibitors of catechol-O-methyltransferase (COMT) can effectively reduce plasma Hcy levels,[24] in the present study, we did not plan to recruit patients on stable therapy with COMT inhibitors; however, our study's next steps will include the assessment of the putative protective role of COMT inhibition on the development of neuropathy and the clinical and electrophysiological follow-up of PD patients with neuropathy after adequate supplementation therapy.

We decided to assess neuropathy by means of both clinical and electrophysiological measures using a blinded procedure; however, blinding is extremely difficult in this setting and, for obvious reasons, only neurophysiologists, but not neurologists, were blinded to the existence of clinical features of neuropathy or disease treatment (exposure and time of exposure to L-dopa or drug doses in patients with PD). In previous reports, either investigators were not blinded with regard to the patient's condition[1,2] or the unblinded assessment was carried out only on a clinical basis.[3] Because we were aware that the diagnosis of peripheral neuropathy based only on clinical grounds might be difficult because of the wide overlapping of PD-related symptoms and neuropathy-related complaints (pain, paraesthesias, sensory symptoms, and impaired balance), we defined patients and controls as neuropathic when there was an abnormal electrophysiological parameter in at least one of the explored nerves, but the diagnosis had to be confirmed on clinical grounds. In all neuropathic patients, we observed a reduction of sural nerve amplitude, which was proportionally more relevant than the common peroneal CMAP reduction. Similarly, the impairment of the

sensory item on the rTNS was greater than that of the motor item (which was normal or only slightly abnormal in the large majority of the neuropathic patients). Taken together, the clinical and electrophysiological features of the neuropathic patients were consistent with a predominantly sensory neuropathy. On the other hand, we are aware that the criteria chosen for the diagnosis of neuropathy in the present study were selective, and both asymptomatic and small fiber neuropathies could have been under diagnosed (the former lacking the criteria for neuropathy-related complaints, and the latter lacking the electrophysiological criteria).

In summary, we observed a significantly greater prevalence of neuropathy in patients with PD compared with healthy controls, and there was a significant relationship of time and, to a lesser extent, dose exposure to L-dopa. To date, the clinical relevance of sensory neuropathy in the context of PD motor disability had not been previously assessed. Our findings of an association between neuropathy and postural instability might highlight the effect of peripheral involvement in worsening PD motor impairment. Because the postural imbalance due to neuropathy-related sensory disturbances can be treated by specific rehabilitative protocols, which may differ from those classically adopted for PD, the early detection and management of neuropathy in the course of PD might have great clinical relevance.

The positive association between neuropathy, low serum vitamin B12 levels, and mainly high serum Hcy levels could be related to L-dopa exposure (in terms of duration and, presumably, daily amount) in predisposed individuals. Periodic Hcy, vitamin B12, and folate screening, together with serial clinical and neurophysiological assessment for neuropathy, may be advisable in patients with PD who are receiving L-dopa treatment. We cannot exclude the possibility that the lack of other detoxificant factors, such as vitamin B6 either alone or in combination with vitamin B12 deficiency, as recently described in two cases of PD with axonal neuropathy in patients receiving duodopa treatment,[9] could play a role in altering peripheral nerve homeostasis. However, the dietary supplementation of vitamin B6 is not advisable in patients with PD because of the potential interference with L-dopa metabolism.

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