Neuropathy in Parkinson disease : Prevalence and determinants

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Neuropathy in Parkinson disease

Prevalence and determinants

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ABSTRACT

Objective: To ascertain the prevalence and determinants of neuropathy in patients with Parkinson disease (PD), in particular, the roles of vitamin B_{12} and levodopa exposure.

Methods: We performed a cross-sectional study of 37 patients with PD and 37 age- and gender-matched controls, using a sensitive and validated neuropathy scale. The prevalence of neuropathy was determined and compared between groups. We then ascertained the role of vitamin B_{12} by a separate case-control analysis 1) comparing numbers of patients in whom the neuropathy was directly attributable to vitamin B_{12} deficiency and 2) comparing serum vitamin B_{12} levels in patients with PD with neuropathy with a second control group consisting of age- and gender-matched consecutive patients with neuropathy without PD. We also determined correlations between cumulative levodopa exposure, PD duration, neuropathy status and score, and vitamin B_{12} status and levels in all patients with PD and, specifically, in those with neuropathy.

Results: Fourteen of 37 (37.8%) patients with PD and 3 of 37 (8.1%) control subjects had neuropathy ($p = 0.005$), corresponding to an odds ratio (95% confidence interval) for neuropathy, of 6.9 (1.78–26.73). Vitamin B_{12} deficiency was a significantly more common cause of neuropathy ($p = 0.024$) and vitamin B_{12} levels were significantly lower ($p = 0.002$) in patients with PD with neuropathy than in age- and gender-matched consecutive control subjects with neuropathy without PD. Cumulative levodopa exposure correlated with PD duration ($p = 0.001$) and vitamin B_{12} levels ($p = 0.044$), in patients with PD with neuropathy.

Conclusions: Neuropathy is more prevalent in patients with PD than in control subjects. This may be predominantly due to vitamin B_{12} deficiency, which could relate to cumulative levodopa exposure in susceptible individuals. Vitamin B_{12} monitoring and supplementation, as well as serial clinical assessment for neuropathy, may be advisable in patients with PD. *Neurology*® 2011;77:1947–1950

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **IGT** = impaired glucose tolerance; **MMA** = methylmalonic acid; **OR** = odds ratio; **PD** = Parkinson disease; **UENS** = Utah Early Neuropathy Scale.

Neuropathy has recently been described in significantly higher proportions in patients with Parkinson disease (PD) than in control subjects.[1] This finding was hypothesized to relate to levodopa therapy and consequent vitamin B_{12} deficiency.[1,2] Furthermore, there are anecdotal reports of duodopa-induced vitamin B_{12} deficiency and neuropathy.[3,4]

We aimed to ascertain in a consecutively selected sample of patients with PD the prevalence and determinants of neuropathy. The roles of vitamin B_{12} and cumulative levodopa exposure were specifically evaluated in the light of recent literature.[1,2] We also studied the influence of other potential causes of neuropathy.

Editorial, page 1938

CME

Patient Page

METHODS We conducted between October 2010 and February 2011 a cross-sectional study of consecutively selected patients with idiopathic PD attending our institution's specialist clinic. Peripheral nerve function was evaluated unblinded using a sensitive and validated neuropathy scale, the Utah Early Neuropathy Scale (UENS),[5] with a predetermined cutoff score of ≥5 of 42 for a positive diagnosis. We determined serum vitamin B_{12} levels, PD duration, cumulative levodopa exposure, body mass index (BMI), and alcohol consumption in all. For those with neuropathy, we performed further blood investigations (including full blood count,

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C-reactive protein, electrolytes, renal function, liver enzymes, γ-glutamyl transferase, folate, vitamin B_1, vitamin B_6, thyroid function, glucose tolerance, and serum protein electrophoresis) and electrophysiology (unilateral median, ulnar, fibular, and tibial motor and unilateral median and radial and bilateral sural sensory nerve conduction studies). We similarly recruited age-matched (±5 years) and gender-matched control subjects from consecutive patients without PD attending our institution during the same period. Control subjects found to have neuropathy also underwent the above-mentioned investigations. We considered preexisting neuropathy, diabetes, vitamin B_{12} deficiency, and chronic alcoholism as exclusion criteria for both groups.

We then compared patients with PD with neuropathy exclusively for the role of vitamin B_{12} in a case-control analysis with a second control group of patients with known acquired distal axonal neuropathy consecutively attending our institution's neuromuscular clinic. This control group consisted of 2 consecutive age- and gender-matched patients for each patient with PD with neuropathy. The proportion of patients for whom vitamin B_{12} deficiency was established as the only possible underlying cause (defined for the purposes of this analysis as vitamin B_{12} level <300 ng/L in absence of any other detectable cause of neuropathy)[6] were compared between groups. Mean serum vitamin B_{12} levels were also compared. Finally, we determined intercorrelations between cumulative levodopa exposure, PD duration, vitamin B_{12} status and levels, and neuropathy status and UENS scores in all patients with PD and, specifically, in those with neuropathy.

The primary outcome measure was prevalence of neuropathy. One previous study revealed a minimal difference in neuropathy prevalence between patients with PD and control subjects of 31% (47% vs 16%).[1] On that basis, a sample size of 35 patients/group was required for a Fisher exact test (0.05 one-sided significance) to detect such a difference of prevalence with a power of 85%. Statistical analyses were performed using SPSS 16.0 software. Differences in proportion were ascertained by Fisher exact tests and differences of means by *t* tests. Intercorrelations were determined using the Pearson (2-tailed) correlation analysis. Because of their possible influence on neuropathy, vitamin absorption, and levodopa requirements, age, BMI, and alcohol consumption were investigated as potential confounders by intercorrelation analyses with the variables studied.

Standard protocols approval, registrations, and patient consents. This study was reviewed and approved by our institutional review board. Informed written consent was obtained from participants.

RESULTS We screened 42 consenting, consecutively attending patients with PD from a cohort of 954 eligible subjects registered at the specialist clinic. Two were unable to have the full assessment and were excluded. Three patients were excluded as being diabetic or vitamin B_{12}-deficient. Thus, 37 patients with PD (23 male and 14 female) were recruited. Mean age was 67.9 (SD 8.33) years, mean age at onset was 61.95 (SD 8.96) years, and mean disease duration was 5.95 (SD 3.81) years. Likewise, we recruited 37 age-matched (±5 years) and gender-matched neurologic control subjects. The most common diagnoses in control subjects were migraine or headache (10 subjects), epilepsy or blackouts (8 subjects), and myasthenia gravis (7 subjects).

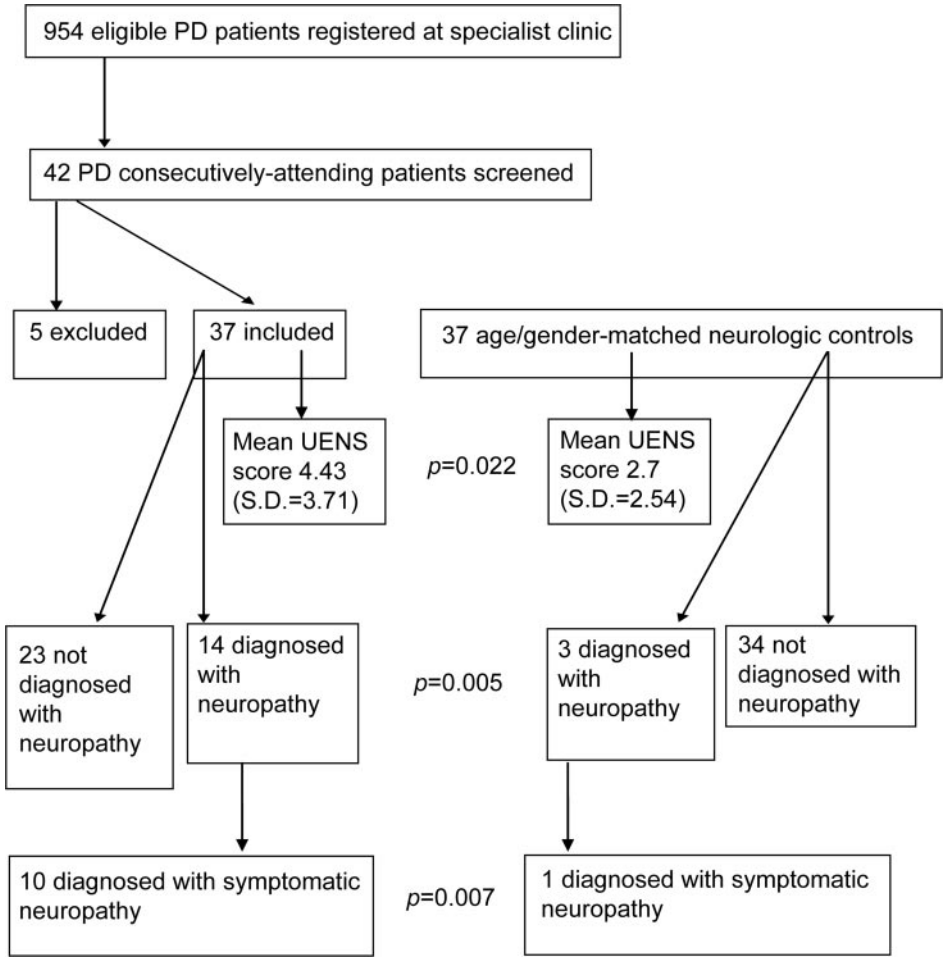
Figure 1 shows the main results. We diagnosed 14 of 37 patients with PD (37.8%) and 3 of 37 (8.1%) control subjects with neuropathy ($p = 0.005$), corresponding to an odds ratio (OR) for neuropathy of 6.9 (95% confidence interval [CI] 1.78–26.73). Ten patients with PD but only 1 control subject had symptomatic neuropathy (OR 13.3, 95% CI 1.61–110.57; $p = 0.007$). The mean UENS score in patients with PD was 4.43 (SD 3.71) vs 2.7 (SD 2.54) in control subjects ($p = 0.022$). Gender did not influence neuropathy occurrence in patients with PD (9 of 23 male, 5 of 14 female; $p = 1$). No patient with PD or control subject took vitamin supplements or had undergone gastric surgery. There were no dietary intake differences between groups or between patients with PD with or without neuropathy. Underlying diagnoses in the 3 control subjects with neuropathy were myasthenia gravis, epilepsy, and migraine. Electrophysiology results were consistent with an axonal process in 9 patients with PD with neuropathy (64.3%) and were normal in 5 patients (35.7%).

Figure 2 illustrates the second analysis. Eight of the 14 patients with PD (57.1%) with neuropathy had vitamin B_{12} levels <300 ng/L, compatible with deficiency. In 1 of these 8, impaired glucose tolerance (IGT) was found as an additional cause of neuropathy. Of the other 6 patients, only 1 had an established cause for neuropathy (IGT). Comparing the patients with PD with neuropathy with the second control group of consecutive subjects with neuropathy without PD, we found vitamin B_{12} deficiency as the sole possible cause for neuropathy in 7 of 14 patients with PD vs 4 of 28 control subjects ($p = 0.024$). Vitamin B_{12} levels were significantly lower in patients with PD with neuropathy than in control subjects (286.8 [SD 84.5] ng/L vs 413.2 [SD 131.7] ng/L; $p = 0.002$).

In considering all patients with PD, cumulative levodopa exposure correlated significantly with PD duration (Pearson correlation 0.673, $p < 0.001$). There were no intercorrelations between cumulative levodopa exposure, vitamin B_{12} status or levels, neuropathy status, or UENS scores. In patients with PD with neuropathy, there were significant correlations between cumulative levodopa exposure and disease duration (Pearson correlation 0.791, $p = 0.001$) and between cumulative levodopa exposure and vitamin B_{12} level (Pearson correlation −0.545, $p = 0.044$) (figure 3). In this subgroup, vitamin B_{12} levels failed to correlate with PD duration ($p = 0.095$). UENS scores did not correlate with vitamin B_{12} levels or with cumulative levodopa exposure. Age, BMI, and alcohol consumption were not identified as potential confounders.

DISCUSSION We found a significantly greater prevalence of neuropathy in patients with PD com-

Figure 1 Comparison of patients with Parkinson disease (PD) and age- and gender-matched neurologic control subjects for neuropathy



UENS = Utah Early Neuropathy Scale.

pared with that in control subjects. Our findings also favor vitamin B_{12} deficiency as probably the most common cause of neuropathy in patients with PD and support the fact that this may relate to levodopa therapy. We ascertained a correlation between cumulative levodopa exposure and vitamin B_{12} levels only

Figure 2 Role of vitamin B_{12} deficiency in Parkinson disease (PD) with neuropathy vs neuropathy without PD

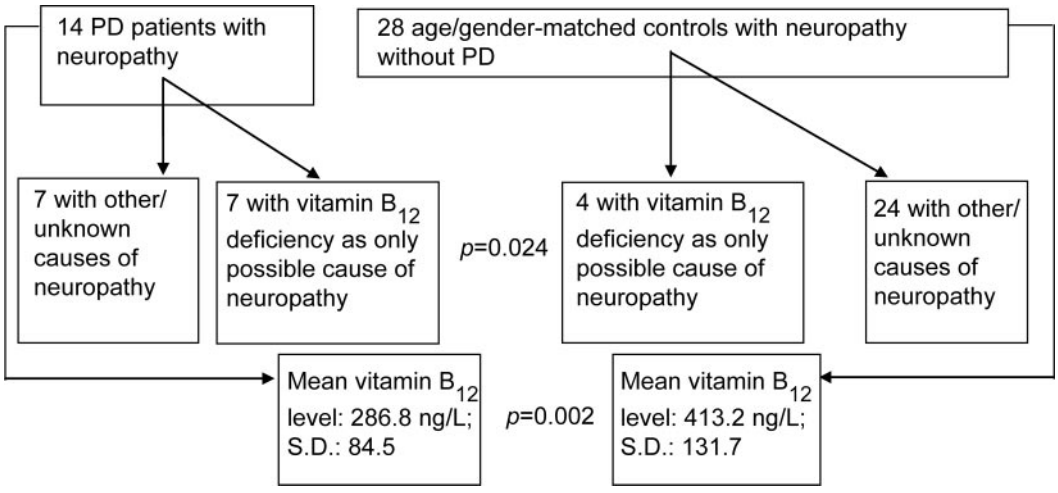
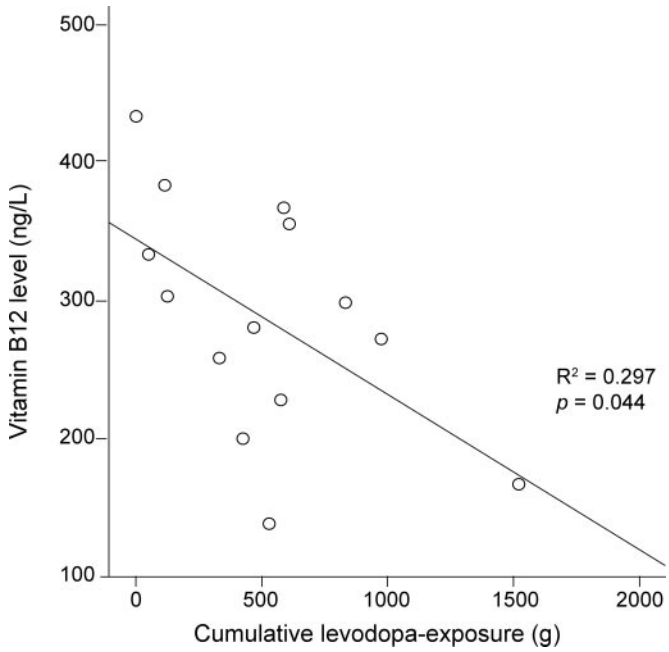


Figure 3 Relation between cumulative levodopa exposure and vitamin B_{12} levels in patients with Parkinson disease and neuropathy



in patients with PD with neuropathy, suggesting that this subgroup may have a susceptibility to deficiency and consequent neuropathy. We were unable to confirm previously described correlations between cumulative levodopa exposure and neuropathy severity.[1] Correlations of neuropathy scores and levodopa exposure have been described with methylmalonic acid (MMA) levels.[1] Our results support the possibility that genetically predisposed patients with PD may develop levodopa-induced vitamin B_{12} deficiency with subsequent neurotoxic MMA accumulation.

The description of the increased prevalence of neuropathy in PD is recent and remains controversial.[1,2,7] Precise underlying pathophysiologic mechanisms implicated also remain debated as are the etiologies and consequences of neuropathy in this population.[8–10] Definite conclusions about determinants are not possible given numbers of patients analyzed in our study, which was powered to assess prevalence. Our analysis may otherwise be limited by potential selection bias in this hospital-based study, use of the UENS for which the reliability outside diabetic or prediabetic neuropathy is unknown,[5] and the cutoff score used. Patients with PD with neuropathy but normal electrophysiology (who all had large-fiber involvement clinically) did not undergo skin biopsy. The unblinded assessment for neuropathy may also have represented a source of bias, although we believe true blinding is unrealistic in this setting because of the clinically obvious appearance of PD. We used a predetermined UENS score cutoff, in an attempt to minimize this bias. Finally, we did not study PD severity or fasting homocysteine or MMA levels and their correlates.

Our results confirm the increased neuropathy prevalence in PD and suggest the practical value of measuring vitamin B_{12} levels in levodopa-treated patients with PD, for whom serial clinical assessments for neuropathy appear justified. Trials of prophylactic replacement therapy may now require consideration.

AUTHOR CONTRIBUTIONS

Dr. Rajabally: conception, organization and execution; design, statistical analysis; writing of manuscript. J. Martey: organization and execution; design; review and critique of manuscript.

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DISCLOSURE

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