Basal Ganglia 6 (2016) 89–94

Contents lists available at ScienceDirect

Basal Ganglia

journal homepage: www.elsevier.com/locate/baga

Prevalence and factors associated with polyneuropathy in Parkinson's disease

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ARTICLE INFO

Article history:
Received 24 December 2015
Received in revised form 13 January 2016
Accepted 20 January 2016
Available online 1 February 2016

Keywords:
Cobalamine
Levodopa
Neuropathy
Parkinson's disease

ABSTRACT

Introduction: Data on polyneuropathy rates in Parkinson's disease vary between studies. Our purpose was to determine its prevalence and the factors associated with that entity.
Material and methods: Presence of polyneuropathy was determined using the Utah Early Neuropathy Scale and a nerve conduction study in patients with Parkinson's disease. We established 2 subgroups of patients with polyneuropathy by clinical relevance: patients scoring ≥5 on the Utah Early Neuropathy Scale, and patients scoring <5 but with a neurophysiological study compatible with polyneuropathy.
Results: Eighty-four subjects were included in the study. Prevalence of polyneuropathy was 30.9%; 21.4% of the patients scored ≥5 and 9.5% scored <5. According to the multivariate analysis, factors associated with polyneuropathy were older age at onset of Parkinson's disease and more advanced stages of the disease according to the Hoehn and Yahr scale. Associated factors were older age and low levels of vitamin B_{12} for the subgroup scoring ≥5, but only age at disease onset for the subgroup with lower scores.
Conclusions: Polyneuropathy may have a primary neurodegenerative origin in relationship with older age at onset of Parkinson's disease and more advanced stages of the disease. Decreases in vitamin B_{12} levels may contribute to exacerbation of polyneuropathy in these patients.

1. Introduction

Several studies have demonstrated the presence of polyneuropathy (PNP) in Parkinson's disease (PD), with a prevalence rate ranging from 11% to 55% [1–4]. PNP has been linked to levodopa treatment as well as to different metabolic alterations in the levels of vitamins B_6 and B_{12}, homocysteine, folic acid, and methylmalonic acid (MMA); these alterations may derive from levodopa use [1–5]. However, reviews by pharmacovigilance networks and systematic reviews of levodopa clinical trials have found no connection between taking oral levodopa and developing PNP [6,7]. Other studies support the hypothesis that peripheral nervous system degeneration may be linked to the aetiopathogenesis of PNP [8–13]. In light of the debates in this field, our purpose was to determine the prevalence of PNP, and its associated factors, in patients with PD.

2. Material and methods

We recruited all consecutive patients with PD attending the movement disorder units and neurology departments of hospitals pertaining to the Zaragoza II health sector, in the region of Aragon, Spain, between April 2012 and October 2014. All included patients had been diagnosed with PD according to the Parkinson's Disease Society Brain Bank diagnostic criteria. Exclusion criteria were as follows: patients treated with deep brain stimulation, continuous apomorphine infusion, or continuous intrajejunal infusion of levodopa–carbidopa intestinal gel; patients previously diagnosed with dementia or scoring ≤24 on the Mini Mental State Examination; patients diagnosed with diabetes mellitus or presenting other known causes of PNP; patients treated with vitamin supplements (B_6, B_{12}, and/or folic acid); patients presenting atypical signs of PD; and patients who did not undergo a neurophysiological study or sign an informed consent form. This study was approved by the Ethics Committee of Aragon Institute of Health Sciences.

A general neurologist based at Hospital Universitario Miguel Servet in Zaragoza, performed the clinical evaluations of all patients and gathered epidemiological data (age at evaluation, age

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http://dx.doi.org/10.1016/j.baga.2016.01.005
2210-5336/

at PD onset, disease duration, sex, and body mass index). We used the Mini Mental State Examination to screen patients for dementia before including them. Data on anti-parkinsonian drugs (levodopa, dopamine agonists, catechol-*O*-methyltransferase inhibitors, rasagiline, or amantadine) were also gathered and the cumulative dose of levodopa was calculated. We divided levodopa exposure into those treated with ≥300 mg/day of levodopa (high daily dose of levodopa), and those treated with ≤300 mg/day of levodopa (low daily dose of levodopa). Disease severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr scale (HY scale), and the Schwab and England Activities of Daily Living Scale. We checked for sensory and motor symptoms compatible with PNP; PNP was diagnosed clinically using the Utah Early Neuropathy Scale (UENS) [14].

After that step, all patients underwent a protocolised neurophysiological assessment in the neurophysiology department at Hospital Universitario Miguel Servet. Researchers were blinded to clinical data. The study protocol included a sensory nerve conduction study of both sural nerves, as well as a motor nerve conduction study of the peroneal and posterior tibial nerves bilaterally. Patients with at least one nerve affected bilaterally were diagnosed with PNP. Lesions were considered demyelinating when the sensory nerve conduction study revealed conduction velocity alterations (<75% of the lower limit of normal) or when patients presented at least 2 of the following motor nerve alterations: homogeneous decrease in conduction velocity (<75% of the lower limit of normal), motor distal latency >130% of the upper limit of normal, increased temporal dispersion, presence of conduction blocks, or increased/absent F-wave latency. Patients were considered to present axonal damage when they exhibited loss of amplitude of nerve action potentials, normal-to-low conduction velocity (although >75% of the lower limit of normal), and normal-to-slightly prolonged motor distal latency (although <130% of the upper limit of normal) [15].

Once the neurophysiological study had been completed, patients were considered to have PNP if results were abnormal and/or if they had scored ≥5 on the UENS. Two different subtypes of PNP were established: a more severe form (scores ≥5 on the UENS: PNP-UENS ≥ 5) and a less severe form (scores <5 on the UENS but with electrophysiological alterations compatible with PNP: PNP-UENS < 5). The PNP-UENS ≥ 5 subgroup was divided into 2 subtypes according to whether or not electrophysiological study results were compatible with PNP (electrophysiological PNP-UENS ≥ 5 and non-electrophysiological PNP-UENS ≥ 5).

Patients included in our study underwent analyses to determine their levels of vitamins B_6 and B_{12}, folic acid, and MMA. Results from an MMA analysis in 7 patients and vitamin B_6 analysis in 9 patients were not included in the quantitative analysis since they had been taken in our hospital. Results from an MMA analysis in 2 patients and vitamin B_6 analysis in one patient were not included in the qualitative analysis due to failures in the processing of the samples. All patients underwent a complete blood count and a biochemical study for electrolytes, TSH, T4, urea, creatinine, folic acid, GGT, GOT, GPT, and LDH; a total protein test; and HIV testing to find other potential causes for PNP. Likewise, we screened for diabetes according to the fasting baseline glycaemia and glycosylated haemoglobin levels established by the American Diabetes Association [16]. Screening for pre-diabetes also drew from ADA criteria for glycosylated haemoglobin and from the World Health Organization criteria for fasting glycaemia levels [17].

Statistical analysis was performed using SPSS statistical software version 15.0. Firstly, we performed a descriptive analysis of the variables recorded above. A bivariate analysis was subsequently conducted to determine the variables associated with presence of PNP and its different subtypes. The *t*-test was used to establish the connection between dichotomous qualitative variables and quantitative variables. The Mann–Whitney *U* test was used when variables were not normally distributed. The correlation study for quantitative variables consisted of the Spearman rank correlation coefficient for non-normally distributed variables. The chi-square test was used to analyse categorical variables, and the Fisher exact test was used when at least 80% of the expected cell values in the contingency table were ≤5. Statistical significance was set at $p < 0.05$. Variables showing a statistically significant difference in risk of developing PNP in the bivariate analysis or shown to be significant in previous studies were included in the logistic regression model for the multivariate analysis.

3. Results

We included 84 patients in our study. A total of 8 patients were previously excluded for the following reasons: 2 scored ≤24 on the Mini Mental State Examination, 2 refused the neurophysiological study, 2 were taking vitamin supplements at time of the assessment, one was abusing alcohol (which would alter results from the metabolic study), and one developed signs compatible with progressive supranuclear palsy during the follow-up. Final prevalence of PNP was 30.9% ($n = 26$); 21.4% of patients ($n = 18$) had PNP and scored ≥5 on the UENS, and 61.1% of them ($n = 11$) also met neurophysiological criteria. The PNP-UENS < 5 group comprised 9.5% of the patients ($n = 8$). All patients with a neurophysiological study indicative of PNP exhibited an axonal pattern: 57.8% presented sensory-motor PNP ($n = 11$), 36.8% had sensory PNP ($n = 7$), and 5.2% had motor PNP ($n = 1$). Findings from the neurophysiological study are shown in Supplementary Table 1.

Three patients with PNP (11.5%) showed metabolic alterations traditionally regarded as responsible for PNP: diabetes mellitus ($n = 2$) and pre-diabetes ($n = 1$). Two of these patients presented high levels of homocysteine. In 12 patients (46.2%), the only potential cause of PNP was presence of altered levels of homocysteine, MMA, and/or vitamins B_6 or B_{12} according to the metabolic study. In other 11 patients (42.3%), we found no factors that might potentially be associated with developing PNP (Supplementary Table 2).

According to the bivariate analysis, mean ages at evaluation and at PD onset were significantly higher in patients with PNP than in patients without the disease. The cumulative dose of levodopa was significantly higher in PNP-UENS ≥ 5 patients than in those in the PNP-UENS < 5 group (Table 1). There were no significant differences in the use of dopamine agonists, catechol-*O*-methyltransferase inhibitors, rasagiline, or amantadine between patients with PNP and patients without PNP. Stages on the HY scale were significantly higher in the PNP patient group and the PNP-UENS ≥ 5 subgroup than in patients without PNP. Scores on the UPDRS-III were higher in the PNP-UENS ≥ 5 group than in patients without PNP (Table 2). Mean vitamin B_{12} levels were significantly lower in patients in the PNP-UENS ≥ 5 group than in patients without PNP. No statistically significant differences were found in any of the other parameters (Table 3). Mean homocysteine levels were only significantly higher in the PNP-UENS ≥ 5 subtype with electrophysiological impairment (16.9 [SD 4.6] μmol/L vs. 13.5 [SD 4.6], $p = 0.031$). Findings from bivariate analysis of PNP-UENS ≥ 5 electrophysiological and non-electrophysiological subtypes are shown in Supplementary Table 3.

UENS score was significantly correlated with ages at evaluation ($r = 0.428$, $p = 0.000$) and at PD onset ($r = 0.369$, $p = 0.001$), cumulative dose of levodopa ($r = 0.237$, $p = 0.030$), HY scale ($r = 0.485$, $p = 0.000$), Schwab and England ($r = -0.368$, $p = 0.001$), UPDRS score ($r = 0.360$, $p = 0.001$) and levels of MMA ($r = 0.229$, $p = 0.049$) and homocysteine ($r = 0.239$, $p = 0.028$). No significant correlations were found between UENS score and disease duration, level of of vitamin B_{12}, B_6 and folic acid.