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Abstract

Background Although peripheral neuropathies (PN) have been described in patients with Parkinson's disease (PD) treated with oral dopaminergic therapies, anecdotal reports of subacute severe PN have been reported during treatment with enteral levodopa/carbidopa infusion (Duodopa).

Aim of the study We prospectively assessed clinical and electrophysiological data of 15 consecutive patients with PD treated with Duodopa for a mean follow-up of 9 months.

Methods Nerve conduction studies and a clinical evaluation with a standardized battery of peripheral neuropathy scales were performed at baseline and after a mean follow-up of 9 months.

Results At baseline, mild signs of PN were observed in three subjects, and vitamin B12 serum levels were found to correlate with the amplitude of sural sensory action potentials. Follow-up data were available for 10/15 subjects: one patient developed a subacute sensory-motor PN and three subjects with pre-existing PN showed a moderate worsening of electrophysiological and clinical features. Subclinical electrophysiological alterations of peripheral nerves were observed in two subjects. No significant changes were observed in vitamin B12, folate, homocysteine and methylmalonic acid levels.

Conclusions In this consecutive series of patients treated with Duodopa, we observed one subacute sensory-motor PN and few length-dependent alterations of peripheral nerves, similar to those described during oral levodopa treatment.

Introduction

Peripheral neuropathies (PN) have been described in patients with Parkinson's disease (PD) treated with oral levodopa [1, 2]; Toth and colleagues [1] reported higher incidence of PN in PD subjects vs controls, and Rajabally and Martey [2] observed a correlation between plasmatic levels of vitamin B12 (Vit B12) and PN in PD.
Moreover, some cases of PN have been described in patients treated with enteral levodopa/carbidopa gel infusion (Duodopa) [3-6], raising the question of whether this mean of levodopa administration could be associated with an higher risk of developing PN, possibly because of vitamin adsorption deficiency or immune-mediated responses [3-7]. Nevertheless, no prospective data have been reported on patients undergoing Duodopa treatment, and the real prevalence of this adverse events is far to be clear, because neurophysiological systematic evaluations have not been performed yet. At the present time, only hypotheses can be deduced on the pathogenesis of isolated cases described in literature: Antonini et al. [3] observed a case of severe PN not responding to plasmapheresis after 7 months of Duodopa treatment, Manca et al. [4] reported a case of encephalopathy and axonal neuropathy responsive to Vit B12 administration after 4 months of treatment. In addition, Urban et al. [5] described two cases of acute PN, both after 13 months of Duodopa therapy, which significantly improved after Vit B6 and Vit B12 supplementation and Klostermann et al. [6] two cases of severe PN with increased homocysteine (Hcy) and decreased Vit B6 and folate plasmatic levels after less than 3 months since the start of Duodopa infusion.

Here, we report the prospective clinical and electrophysiological assessment of 15 consecutive patients treated with Duodopa infusion for an average follow-up period of 9 months.

**Materials and methods**

Clinical and electrophysiological assessments were carried out in 15 consecutive patients with PD (7 males and 8 females) treated with Duodopa at our centre between July 2010 and September 2011, both before the placement of Duodopa intestinal tube and after approximately 9 months (±3 months) since the start of Duodopa infusion.

Patients were evaluated with the Unified Parkinson's disease rating scale (UPDRS) [8], Overall Neuropathy Limitation Scale (ONLS) [9], Medical Research Council Sum Score (MRCSS) [10] and Incat Sensory Sum Score (IncatSSS) [11]. Nerve conduction studies (Keypoint, Alpine biomedical) were obtained for the bilateral peroneal, ulnar and median motor nerves and for the bilateral sural, median and ulnar sensory nerves, investigating distal latencies, amplitudes and nerve conduction velocities, according to the normality cut-off values reported by Kimura [12]; all patients were checked for skin temperature with a probe on the EMG machine, and an infrared heating element was used if necessary. Moreover, a standardized routine blood and urinary work was performed at baseline to rule out possible causes of PN [1]; Vit B12 (normal values >200 pg/ml), folate (normal values >4.6 ng/ml) and Hcy (normal values <20 μm) were reassessed at follow-up, as well as methylmalonic acid (MMA) urinary levels (normal values <5 μmol/mmol creatinine).

Statistical analyses were performed with PaswStat 18 for Windows, using Wilcoxon rank-sum test, Pearson (2-tailed) correlation analysis and multivariate Cox regression model. All P-values reported are two-tailed, considering 0.05 as statistical threshold. All subjects gave written informed consent to be anonymously included in the study.
Results

One subject was excluded after the first examination, before the placement of Duodopa enteral tube, because of diabetes mellitus type II (Fig. 1). The mean age at surgery of the remaining 14 subjects was 69.6 ± 6.2 years old (range: 58–78), and the average disease duration was 14.1 ± 4.5 years (range: 8–24).

Baseline clinical, biochemical and electrophysiological data

At baseline, mild clinical signs of PN, associated with electrophysiological sensory-axonal alterations, were found in 3/14 subjects (21.4%) (Fig. 1). In one of these three cases, Vit B12 plasmatic levels were lower than normal (153 pg/ml), and Hcy plasmatic levels were increased (40.1 μm). No significant blood tests alterations were observed in the other cases. A correlation was observed between sural sensory nerve action potentials (SAP) amplitude and Vit B12 plasmatic levels ($P = 0.025$), and between sural SAP amplitude and age ($P = 0.01$).

Follow-up clinical, biochemical and neurophysiological data

As shown in Fig. 1 patients dropped out (one returned to oral levodopa therapy for personal preferences, and three subjects did not repeat the electrophysiological assessment), and follow-up data were available for the remaining 10/14 patients after 8.9 ± 2.3 months (range 6.3–11.6 months) of Duodopa treatment.

The average UPDRS-III score decreased from 40.88 ± 14.8 in medication-OFF baseline condition to 26.75 ± 11.62 in Duodopa daily-ON condition ($P = 0.02$), and the average UPDRS-IV score significantly improved from 8.66 ± 2.63 to 4.57 ± 1.35 ($P = 0.03$).
The mean levodopa-equivalent daily dose (LEDD) increased moderately from 1120.8 ± 473.7 to 1281.8 ± 289.6 mg/day (P = 0.51). No significant alterations were observed in the levels of folate (6.6 ± 2.2 [RIGHTWARDS ARROW] 5.4 ± 2.4 ng/ml; P = 0.11) and Hcy (42.3 ± 53.3 [RIGHTWARDS ARROW] 43.4 ± 18.6 μm; P = 0.89) or in the urinary MMA values (1.2 ± 0.6 [RIGHTWARDS ARROW] 2.1 ± 1.7 μmol/mmol creatinine; P = 0.18), while a moderate decrease was observed in Vit B12 plasmatic levels (358.9 ± 160.3 [RIGHTWARDS ARROW] 257.9 ± 55.2 pg/ml; P = 0.068).

One patient, without any clinical or electrophysiological alteration at baseline, developed a severe subacute sensory-motor multineuropathy after 4 months of Duodopa treatment, associated with a relevant increase in the IncatSSS (0[RIGHTWARDS ARROW]10) and ONLS score (1[RIGHTWARDS ARROW]5) and a decrease in MRCSS (56[RIGHTWARDS ARROW]48); nerve conduction studies (Fig. 2) showed prolonged distal motor latencies, motor nerve conduction blocks (CMAP amplitude decrease >30%) in both peroneal and ulnar nerves, and reduced nerve conduction velocities (NCV) of sensory and motor nerves, in the range of demyelination. No significant alterations were found in MMA, Hcy and Vit B12 levels. Moreover, a lumbar puncture was performed, revealing normal proteinorachia and cerebrospinal fluid cellularity. Duodopa treatment was interrupted, and the patient was switched back to oral levodopa therapy with a supplementation of Vit B1, Vit B12 and folate. A partial recovery of clinical symptoms was observed after one month, and a gradual improvement of nerve conduction studies was found in two consecutive assessments, performed after two and 5 months (Fig. 2).
The mean sural SAP amplitude of the remaining nine subjects decreased from 8.9 ± 3.2 μV (baseline) to 6.7 ± 3.2 μV (P = 0.022), while the mean sural NCV ranged from 49.8 ± 4.6 m/s (baseline) to 45.2 ± 7.3 m/s (P = 0.025). Only mild changes were observed in upper limbs nerve conduction studies, and no significant association were revealed between age, gender, PD duration, LEDD or duration of Duodopa infusion and the hazard ratio of developing PN.

The three subjects with a pre-existing PN at baseline developed a mild worsening of clinical and electrophysiological features; the ONLS ranged from 3.0 ± 1.0 to 3.7 ± 1.5, the IncatSSS from 5.3 ± 1.5 to 6.7 ± 1.2 and the sural SAP amplitude decreased from 4.7 ± 0.5 to 3.5 ± 0.5. Moreover, 2 subjects without clinical or electrophysiological alterations of peripheral nerves at baseline developed moderate alterations of nerve conduction studies during the follow-up (the sural SAP amplitude decreased from 7.9 ± 1.4 to 4.9 ± 0.2), not associated to clinical correlates. Only minimal alterations of nerve conduction studies were observed in the remaining four subjects (sural SAP amplitude ranging from 11.9 ± 1.2 to 9.9 ± 0.6).

Discussion

To our knowledge, this study represents the first prospecational assessment of PN in Duodopa-treated patients. We described a cohort of patients with PD starting Duodopa treatment, comparing their baseline clinical and electrophysiological values with those obtained after an average follow-up period of 9 months.

At baseline, moderate signs of PN were observed in 21.4% of subjects, in agreement with literature data reporting high prevalence of PN in patients with PD treated with oral levodopa [1, 2].

Moreover, similarly to Rajabally and Martey [2], we observed a significant correlation between electrophysiological alterations and Vit B12 plasmatic levels, possibly supporting a correlation between Vit B12 deficiency and the chronic, insidious development of axonal PN.

On the other side, one patient developed a subacute severe sensory-motor multineuropathy, with prolonged distal motor latencies, motor nerve conduction blocks and reduced nerve conduction velocities. It could be hypothesized that immune-mediated responses or, alternatively, an acute vitamin adsorption deficiency might have played a role in the pathogenesis of this case, which resembles other PN reported in patients treated with Duodopa [3-6].

Among the remaining 9 subjects, a worsening of peripheral nerve conduction studies was observed in five cases (3 of them were already affected by a moderate PN at baseline) showing a mild axonal length-dependent PN similar, to some extent, to those described with oral levodopa treatment [1, 2]. This finding may suggest an alternative pathogenetic mechanisms associated with Duodopa enteral infusion on peripheral nerves. However, as no clear correlation was found with the duration of infusional therapy, and given the significant improvement observed on motor symptoms, Duodopa treatment was not interrupted in these subjects, but a Vit B12 supplementation was administered in case of low serum levels, and a strict clinical and electrophysiological follow-up was prescribed.

In conclusion, the first results of this prospective study suggest that the more frequent peripheral nerves pattern of alterations observed during Duodopa treatment might resemble those described with oral levodopa therapy. However, several limitations should be considered, including the limited observational period, which was maybe not long enough to disclose all the possible adverse events related to Duodopa
infusion, the small sample size and the absence of a control group represented by patients with PD receiving oral dopaminergic treatments.

Nevertheless, similarly to other cases reported in literature [3-6], also in our cohort, one patient developed a subacute PN; at baseline, this subject did not show any clinical, electrophysiological or biochemical alteration that may had been correlated with the following clinical evolution.

As reported by other authors [13], motor symptoms and motor complications significantly improved after the start of Duodopa infusional therapy; however, our findings suggest that peripheral nerves, electrophysiological surveillance and Vit B12 serum controls seem to be advisable during both Duodopa and levodopa treatment.

**Acknowledgment**

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**Conflict of interest**

Nothing to declare.

**References**


