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Prevalence and features of peripheral neuropathy in Parkinson's disease patients under different therapeutic regimens

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ABSTRACT

Background: Recent reports suggest increased frequency of peripheral neuropathy (PN) in Parkinson's disease (PD) patients on levodopa compared with age-matched controls particularly during continuous levodopa delivery by intestinal infusion (CLDII). The aim of this study is to compare frequency, clinical features, and outcome of PN in PD patients undergoing different therapeutic regimens.
Methods: Three groups of consecutive PD patients, 50 on intestinal levodopa (CLDII), 50 on oral levodopa (O-LD) and 50 on other dopaminergic treatment (ODT), were enrolled in this study to assess frequency of PN using clinical and neurophysiological parameters. A biochemical study of all PN patients was performed.
Results: Frequency of PN of no evident cause was 28% in CLDII, 20% in O-LD, and 6% in ODT patients. Clinically, 71% of CLDII patients and all O-LD and ODT PN patients displayed a subacute sensory PN. In contrast, 29% of CLDII patients presented acute motor PN. Levodopa daily dose, vitamin B12 (VB12) and homocysteine (hcy) levels differed significantly in patients with PN compared to patients without PN.
Conclusions: Our findings support the relationship between levodopa and PN and confirm that an imbalance in VB12/hcy may be a key pathogenic factor. We suggest two different, possibly overlapping mechanisms of PN in patients on CDLII: axonal degeneration due to vitamin deficiency and inflammatory damage. Whether inflammatory damage is triggered by vitamin deficiency and/or by modifications in the intestinal micro-environment should be further explored. Proper vitamin supplementation may prevent peripheral damage in most cases.

1. Introduction

Peripheral neuropathy (PN) was recently reported in the context of long term levodopa treatment in patients with Parkinson's disease (PD) [1,2].

Two large studies analyzing PD patients on levodopa showed a relatively high prevalence of PN ranging from 37.8 to 55%, compared with 8.1 to 9% frequency in control subjects [1,2]. The authors suggested a link between imbalance in vitamin B metabolism and PN onset, although there is still no consensus whether this is a biomarker for diagnostic purposes.

Concomitantly, a few reports brought to scientific attention cases of PN in advanced PD patients undergoing continuous levodopa delivery by intestinal infusion (CLDII) [3–7]. CLDII is an effective treatment for advanced PD patients who experience motor and non-motor complications that are not adequately controlled by optimized oral medication regimen [3]. Currently, there are no definite data on the prevalence and features of PN in patients during CLDII.

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Our study aims at assessing prevalence and features of PN in PD patients with different routes of administration of levodopa, compared with PD patients on other dopaminergic medications.

2. Patients and methods

One hundred and fifty patients (86 men, 64 women, mean age 67 years, supplementary Table 1) with a diagnosis of PD according to UK Brain Bank Diagnostic criteria [8], were enrolled in the study. We analyzed three groups of patients treated with: 1) Levodopa intestinal infusion (CLDII); 2) Oral levodopa (O-LD); 3) Other dopaminergic therapy (ODT), such as dopamine agonists, alone or in combination with monoamino-oxidase B inhibitors.

CLDII patients were consecutively recruited since January 2009 at the following Italian Movement Disorder Centres: San Pio X Clinic in Milan, Neurological Institute IRCCS "C. Mondino" in Pavia, University of Insubria in Varese, Amedeo Avogadro University in Novara and Mauriziano Hospital in Turin.

These Centers are experienced for CLDII treatment and share a common database in which clinical, neurophysiological, and laboratory findings are collected, according to previously agreed standardized criteria. Enrollment ended September 2011 when we reached 50 patients.

CLDII was started in PD patients presenting with severe motor and non-motor complications, which could not be further improved by oral therapy. The treatment consisted in the administration of a water-based suspension containing micronised levodopa (20 mg/mL) and carbidopa (5 mg/mL) in carboxymethyl cellulose (Duodopa, AbbVie) administered through a transabdominal port. Mean duration of CLDII treatment was 2.86 years (sd 2).

In September 2011 we started recruitment of O-LD and ODT patients at Movement Disorders Centers of San Pio X Clinic in Milan and Amedeo Avogadro University in Novara. Enrollment ended in December 2011.

Both O-LD and ODT groups included the first 50 consecutive patients, with the exclusion of patients whose age was either below the mean −2 SD or above the mean +2 SD of group one patients. Patients' gender was randomly distributed and there were no statistically significant differences among groups.

We performed a cross-sectional analysis that had the presence of PN of no evident cause as primary endpoint. All the following criteria had to be satisfied: 1) history of symptoms suggestive of PN, 2) Exclusion of other medical conditions known for causing PN (diabetes, toxin exposure, alcoholism, hereditary neuropathies, inflammatory neuropathies, metabolic disturbances, paraproteinemia and neoplasms, 3) clinical confirmation with targeted neurological examination, 4) neurophysiological confirmation according to established criteria [9,10], 5) review and confirmation of history, examination and neurophysiological findings by a second neurologist blind to patients' therapeutic regimen (Fig. 1).

Secondary endpoints were: 1) clinical and neurophysiological characterization of PN (PN was defined as acute if symptoms nadir was reached within 4 weeks, and subacute PN if nadir was reached between 4 and 8 weeks), 2) correlation between

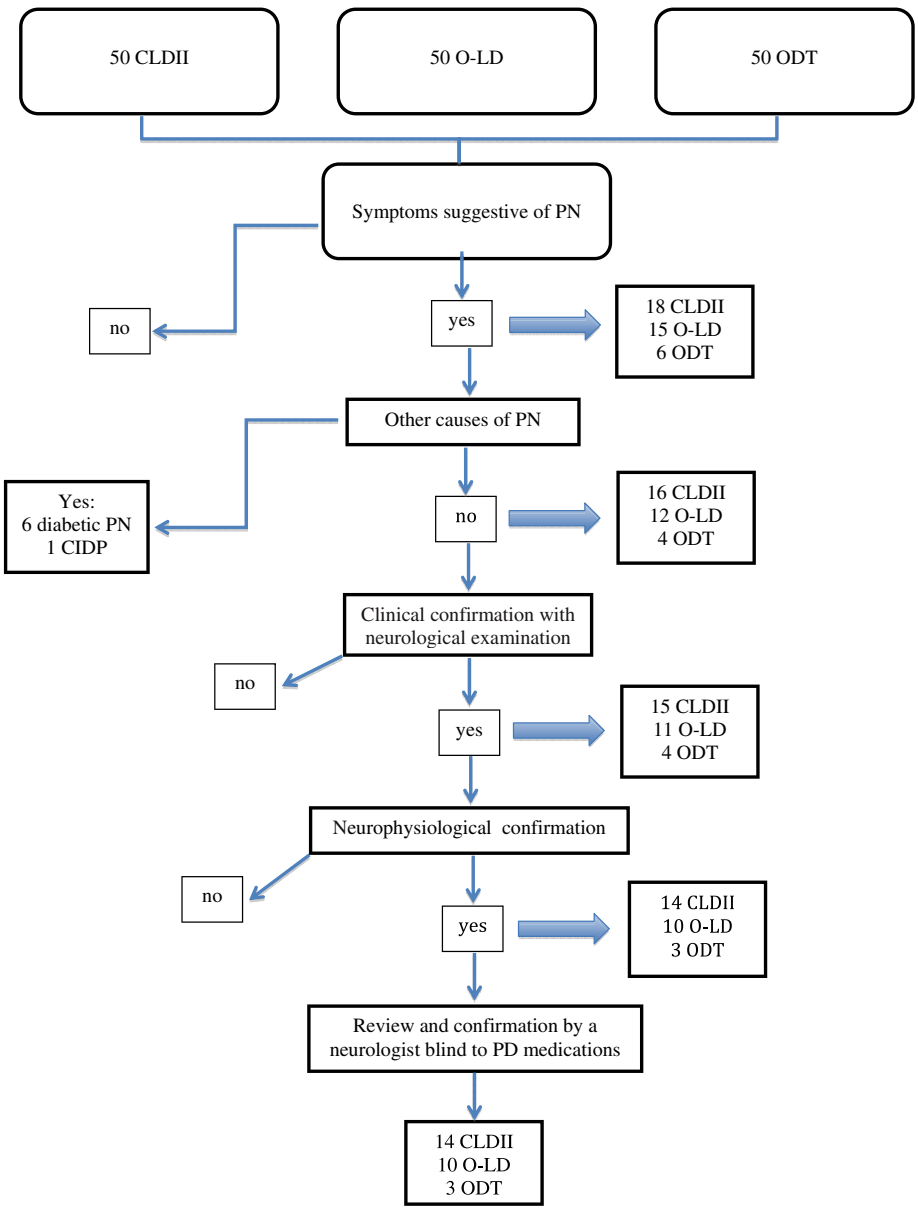

Fig. 1. Diagnostic flow-chart to determine the presence of a peripheral neuropathy. CLDII: continuous levodopa delivery by intestinal infusion, O-LD: oral levodopa, ODT: other dopaminergic therapy, PN: peripheral neuropathy, CIDP: chronic inflammatory demyelinating disease.

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