Peripheral neuropathy in Parkinson’s disease

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Abstract

BACKGROUND: Recent studies suggest an increased frequency of peripheral neuropathy (PN) in Parkinson’s disease patients (PD) (Toth et al. 2010). The aim of our study is to verify the increased frequency of PN in our group of PD patients compared to an age-matched control group. We sorted patients according to the duration of L-DOPA treatment, L-DOPA dosage, and age below or over 50 years.

METHODS AND RESULTS: We conducted electromyography examinations (using conduction studies and needle electromyography) of 49 PD patients with asymptomatic polyneuropathy and 40 controls. Patients without risk factors for PN were included (fasting blood was analyzed to rule out possible causes of PN), as were relatively healthy controls without risk factors for PN. PN was defined using the American Academy of Neurology and Electrodiagnostic Medicine criteria (England et al. 2005).

CONCLUSION: The frequency of polyneuropathy was significantly higher in PD patients than in controls (45% versus 2%, p<0.0001). We did not establish a relationship in the PD group according to long-term L-DOPA usage, PD duration, or age. It should be assumed that a neurodegenerative process underlies the involvement of the central and peripheral nervous systems in PD patients.

INTRODUCTION

Involvement of the peripheral nervous system (PNS) is relatively common in some neurodegenerative proteinopathies of the brain and may be pathogenetically and diagnostically important. In PD, neuronal α-synuclein aggregates are redistributed throughout the nervous system, including the central nervous system, sympathetic ganglia, enteric nervous system, cardiac and pelvic plexuses, submandibular gland, adrenal medulla, and skin. The pathological process may target the PNS and CNS at the same time (Wakabayashi et al. 2010).

The aim of our study is to verify the increased frequency of PN in a group of PD patients as compared to an age-matched group of controls.

PATIENTS AND METHODS

The study protocol, including electromyography (EMG) examination, was approved by the Ethics Committee of Palacky University in Olomouc. All
patients gave their informed consent prior to the invasive procedures.

Statistical analysis
The statistic software SPSS version 15 (SPSS Inc., Chicago, USA) was used for the analysis. The files were compared using Fisher’s exact test and in quantitative parameters using the Mann-Whitney U test. The normality data were verified using the Shapiro-Wilk test, and the tests were made at a significance level of 0.05.

Patients
49 patients with PD were examined. PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria (UKPDBB) (Braak et al. 2003; Kingsbury et al. 2010). The group of patients comprised 27 males (55.1%) and 22 (44.9%) females. In males, the mean age was 62 years. In females, the mean age was 68.5 years. The mean age at the start of the disease was 56.4; the mean disease duration was 6 years.

Characteristics of patients in connection with duration of L-Dopa treatment into two groups to 5 years of duration and over 5 years of the duration. In the first group there were the mean age 61.87, the mean age at the start of disease 56.4, and the duration of the disease 5.1 years. In the second group there were the mean age 61.74 years, mean age at the start of the disease 52.63 and the duration of the disease was 11.58 years.

Characteristics of patients in connection with daily dose of L-Dopa dosage into two groups to 500 mg per day and over 500 mg per day, in the first group was the mean age 61.71 years, the mean age at the start of the disease 54.93 years, the duration of the disease 4.14 years, the mean duration of treatment with L-Dopa 1.5 years, in the second group was the mean age 61.86, the mean disease duration 9 years and the mean duration of the treatment was 9 years.

Prior to the neurophysiological examination, a complete neurological assessment was performed in all patients, including MRI brain scan, autonomic function assessment, and biochemical, blood, and cerebrospinal fluid analyses. A biochemical and blood analysis was performed in all patients in the control group. We excluded patients from our study who had hypovitaminosis B12 or systemic disorders such as chronic infections, diabetes or other metabolic diseases, endocrine and autoimmune illnesses, cancer, chronic alcohol consumption, toxic exposure, or any family history of neuropathy.

Controls
The group of controls comprised 40 people, 7 males (17.5%) and 33 (82.5%) females. There were significantly more males in the patient group (55% vs 17%, p=0.0004); patients were significantly younger than controls (median 62 years vs 68, p<0.0001).

Controls were recruited from patients at our Department of Neurology with diagnoses of radicular syndromes; these patients had no history of neurodegenerative diseases or other illnesses that affect the peripheral nerves.

Electrophysiological examination
All patients underwent an EMG examination comprising a nerve conduction study and needle EMG. All tests were performed using the Keypoint IV* system (Medtronic, Tonstakken, Denmark).

The nerve conduction study measured motor conduction of the tibial and deep peroneal nerves and sensory conduction of the superficial peroneal and sural nerves. The needle EMG assessed the activity at rest and recruitment, and the interference curve during maximum effort contraction. The EMG data were entered into an electronic database and statistically processed using StatSoft* software.

PN was defined using the American Academy of Neurology and Electrodiagnostic Medicine criteria for PN (e.g., nerve conduction studies and needle electromyography) (Wakabayashi et al. 2010).

RESULTS
The frequency of PN in our group of PD patients was significantly higher than in the control group (45% versus 5%, p<0.0001). All of the patients with neuropathy had an axonal type of neuropathy, only in one male we found only sensory neuropathy. In the group of patients there were significantly lower parameters, e.g. amplitude n. suralis (p=0.039), sensitive velocity (SCV) n. suralis (p=0.014), amplitude n. tibialis (p=0.006), and motor conduction velocity (MCV) n. peroneus profundus (p=0.007). In comparison depending on age, in the group of patients in the age to 50 years we found only in 1 patient (16.7%) from 6 patients polyneuropathy and in the group of patients in the age over 50 years in 21 patients (48%) from 43 patients.

In comparison depending on disease duration we found in the group with the duration to 5 years the neuropathy in 15 patients (50%) from 30, and in the group with the duration over 5 years only in 7 patients (36.8%) from 19. And the third partition depending on daily amount of L-Dopa to 500 mg per day and over 500 mg per day. In the first group we found neuropathy in 8 patients (57.1%) from 14, and in the second group with dose of L-Dopa over 500 mg per day in 14 (40%) from 35 patients totally. For clarity the results in the Table 1.

DISCUSSION
We divided the PD patients according to their L-DOPA treatment duration, L-DOPA dosage, and age below or above 50 years.

Our first hypothesis concerned dependence on age. We sorted the patients into two groups according to their ages: below or above 50 years. We did not demonstrate a significant difference between the two groups.
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The presence of PN in the neurodegenerative process is a relatively new clinical fact (Nyholm et al. 2005; Manca et al. 2009; Montastruc et al. 2010; Toth et al. 2010; Teodoro et al. 2011; Santos-García et al. 2012; Ceravolo et al. 2013; Jugel et al. 2013; Müller et al. 2013; Rajabally & Martey 2013; Mancini et al. 2014; Merola et al. 2014; Uncini et al. 2014). PN was recently reported in the context of long-term L-DOPA treatment (Montastruc et al. 2010; Toth et al. 2010; Teodoro et al. 2011; Kimber et al. 2013; Rajabally & Martey 2013; Mancini et al. 2014). In two large studies, the occurrence of neuropathy in patients with L-DOPA treatment was found to range from 37.8% to 55%, compared with 8.1% to 9% in control subjects. Toth et al. (2010) postulated the accumulation of cobalamin-related and neurotoxic metabolites consisting of methylmalonic acid (MMA) and homocystein (Hcy). They did not demonstrate a relationship between the level of cobalamin and PN in PD. Up to 50% of cobalamin-deficient patients will have normal serum cobalamin. Rajabally and Martey (2013) examined 37 patients with PD and 37 control subjects; 14 of the 37 (37.8%) patients with PD and 3 of the 37 (8.1%) control subjects had neuropathy (p=0.005). They found a significantly greater prevalence of neuropathy in the patients with PD than in the control subjects. The most common cause they screened was the level of cobalamin.

Teodoro et al. (2011) conducted a systematic review of randomized parallel-design trials that compared marketed antiparkinsonian drugs with placebo (trials published before December 2009). Seventy-nine studies from a total of 795 were included; these studies involved 10, 620 patients treated with L-DOPA and other antiparkinsonian agents, and 6,710 patients treated with placebo. They did not find any reports of neuropathy as an adverse event in the studies involving L-DOPA. They concluded that the safety data from PD clinical trials do not support an association between L-DOPA and neuropathy. This result could be due to the small size of the group of patients under 50.

The second hypothesis concerned L-DOPA treatment duration. We sorted the patients into two groups according to their treatment duration: more or less than 5 years.

We did not find a significant dependence between L-DOPA treatment duration and PN (50% in the group with less than 5 years of L-DOPA treatment; 37% in patients with more than 5 years of L-DOPA treatment).

The third hypothesis concerned the effect of L-DOPA dosage amounts. We sorted the patients into two groups according to their dosage: less than 500 mg per day or more than 500 mg per day. We found a significantly longer duration of PD (median 7 years vs 2.5, p=0.001), significantly longer L-DOPA treatment (med 4 years vs 0, p=0.001) and significantly higher doses of antagonist per day (med 16 mg vs 0 mg, p=0.0002) in the group with L-DOPA dosages over 500mg per day. We found a significantly higher dose of L-DOPA (median 600mg versus 425mg, p=0.039) and significantly lower parameters for MCV n. peroneus (median 44.3 versus 45.8, p=0.046).

We did not find a significant dependence between overall dose of L-DOPA and the occurrence of neuropathy.

Tab. 1. Characteristics of patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=49)</th>
<th>Controls (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>27/22 (55.1% / 44.9%)</td>
<td>7/33 (17.5% / 82.5%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Age</td>
<td>62.0 (29–77)</td>
<td>68.5 (61–85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>H reflex, dx amp. (mV)</td>
<td>1.20 (0–5.6)</td>
<td>1.25 (0.1–5.7)</td>
<td>0.655</td>
</tr>
<tr>
<td>H reflex, dx lat. (ms)</td>
<td>32.0 (0–47)</td>
<td>30.6 (26.5–39.2)</td>
<td>0.364</td>
</tr>
<tr>
<td>H reflex, sin amp. (mV)</td>
<td>1.10 (0–5.0)</td>
<td>1.35 (0.1–3.8)</td>
<td>0.980</td>
</tr>
<tr>
<td>H reflex, sin lat. (ms)</td>
<td>32 (0–42)</td>
<td>31 (26–39)</td>
<td>0.558</td>
</tr>
<tr>
<td>n. suralis dx., amp. (uV)</td>
<td>4.2 (0–20)</td>
<td>6.3 (2–15)</td>
<td>0.039</td>
</tr>
<tr>
<td>n. suralis dx., SCV (m/s)</td>
<td>47.4 (0–63)</td>
<td>51.6 (40–60)</td>
<td>0.014</td>
</tr>
<tr>
<td>n. tibialis dx., DML (ms)</td>
<td>4.1 (0–7.5)</td>
<td>4.2 (3.0–5.7)</td>
<td>0.327</td>
</tr>
<tr>
<td>n. tibialis dx., amp. (mV)</td>
<td>5.0 (0–14)</td>
<td>7.7 (2–13)</td>
<td>0.006</td>
</tr>
<tr>
<td>n. peroneus profundus sin., DML (ms)</td>
<td>4.0 (3–7)</td>
<td>3.9 (2–7)</td>
<td>0.753</td>
</tr>
<tr>
<td>n. peroneus profundus sin., amp. (mV)</td>
<td>3.6 (0.4–9.3)</td>
<td>3.7 (0.7–6.5)</td>
<td>0.808</td>
</tr>
<tr>
<td>n. peroneus profundus sin., MCVp</td>
<td>47.2 (41–57)</td>
<td>44.7 (29–75)</td>
<td>0.034</td>
</tr>
<tr>
<td>n. peroneus profundus sin., MCVn</td>
<td>47.4 (0–60)</td>
<td>50.0 (38–64)</td>
<td>0.007</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>22 (44.9%)</td>
<td>2 (5%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
and neuropathy. Ceravolo et al. (2013) performed a multicenter study of 330 patients with PD and 137 healthy controls. 144 patients had long exposure (over 3 years) to L-Dopa, 103 had only a brief exposure, and 83 patients had no exposure to L-DOPA. They found neuropathy in 19% of the patients in the group with long exposure to L-DOPA, 6.8% in the group with a brief exposure, and 4.82% in the group without L-DOPA exposure; they found 8.76% in the control group. They demonstrated that the duration of exposure to L-DOPA along with age are the main risk factors for the development of neuropathy (Ceravolo et al. 2013). Recent studies have examined the route of administration of L-DOPA (Nyholm et al. 2005; Manca et al. 2009; Santos-Garcia et al. 2012; Jugel et al. 2013; Müller et al. 2013; Mancini et al. 2014; Merola et al. 2014).

Merola et al. (2014) prospectively assessed the data of 15 patients with PD treated with Duodopa for a mean follow-up period of 9 months. In these series of patients treated with Duodopa they observed one acute PN and few length-dependent alterations of peripheral nerves.

This study represents the first prospective assessment of PN in Duodopa treated patients.

Santos-Garcia et al. (2012) described twelve PD patients who developed axonal PN and vitamin B12 deficiency while undergoing treatment with duodenal L-DOPA infusion. L-DOPA gel infusion therapy may induce a decrease in vitamin B12 levels, which can potentially lead to PN. But the level of vitamin B12 was not significant for hypovitaminosis, it was only decreased in comparison (Santos-Garcia et al. 2012).

Müller et al. (2013) reviewed the literature about the occurrence of PN in PD in relation to the route of administration of L-DOPA (Müller et al. 2013). In this review the recipients of Levodopa/carbidopa intestinal gel (LCIG) reflect two general profiles of PN. Slowly progressive axonal type and Guillain–Barré syndrome. In most cases, there are vitamin B12 deficiencies and deficiencies vitamin B6 a folate and an increase in serum homocysteine levels.

So far, in most neurodegenerative diseases, PN has not been thought to be related to the underlying process. Only in multiple system atrophy (MSA) was symmetric polyneuropathy in the lower limbs considered to be a symptom supporting the diagnosis of MSA, in particular MSA-p (Chand et al. 1996; Rossi et al. 1986).

In our study, we did not demonstrate a relationship between the incidence of PN and the dosage of L-DOPA, patient age, or PD duration.

It should be assumed that the neurodegenerative process might underlie the involvement of the central as well as the peripheral nervous system in PD patients. Like the previous authors who studied MSA assumed the underlying pathological process in MSA to be the cause of PN, the neurodegenerative process (in a broad sense) may be considered the cause of PN in our group of PD patients. The mechanism of peripheral neurodegeneration has not yet been explicitly described which is understandable given that neurodegeneration in the CNS is also far from being completely explained.

Limitations of our work is lower number of subjects, which is caused by more rigorous selection of patients with PD, in which we excluded patients with other possible causes of polyneuropathy. A possibility of simultaneous occurrence of PD and PD regardless of the treatment and exogenous factors should be also considered.

Restriction may be also a different gender in the group of patients and controls. The results may also be affected by the higher age of patients, which is commonly associated with various nutritional deficiencies and moreover, they have, due to an interaction with the dopa medication, recommended reduction of milk products in diet. In our group we didn’t investigate level of MMA (methylmalonic acid) and we didn’t include Dopa naïve patients. Additionally, some seemingly independent factors which were correlated with the prevalence of PN in PD may be linked together, such as duration of treatment with L-Dopa and daily dose of L-Dopa.

REFERENCES

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