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Quantitative and fiber-selective evaluation of pain and sensory dysfunction in patients with Parkinson's disease

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ABSTRACT

Introduction: Pain and sensory disturbances affect many patients with Parkinson's disease (PD). The present study aimed to evaluate the pain and sensory sensitivity of each class of afferent fibers in PD patients and determine the effects of dopaminergic therapy on pain and sensory sensitivity.
Methods: Current perception threshold (CPT) and pain tolerance thresholds (PTT) at three frequencies, 2000 Hz, 250 Hz, and 5 Hz, to stimulate Aβ fibers, Aδ fibers, and small C-polymodal fibers, respectively, were measured in 72 PD patients and 35 healthy controls.
Results: CPT was higher at all three frequencies and PTT was lower at 2000 Hz and 250 Hz in PD patients with pain versus healthy controls ($P < 0.05$). CPT was higher at 2000 Hz and 250 Hz and PTT was lower at 2000 Hz and 250 Hz in PD patients without pain versus healthy controls ($P < 0.05$). PD patients with pain exhibited higher CPT at 5 Hz and 250 Hz than PD patients without pain ($P < 0.05$). Dopaminergic therapy did not affect CPT or PPT in PD patients ($P > 0.05$).
Conclusions: Abnormal Aδ fiber- and Aβ fiber-dependent sensory inputs may exist in PD. Abnormal sensory inputs via C fibers and Aδ fibers might be associated with the presence of pain in PD. Because dopaminergic therapy failed to mitigate these sensory and pain dysfunctions, mechanisms not involving the dopaminergic pathway are likely to be implicated.

1. Introduction

Pain and sensory disturbances are common non-motor symptoms of Parkinson's disease (PD) and occur in many patients; these symptoms often have a dramatic negative impact on the patient's quality of life. However, the pathogenesis of pain and sensory disturbances in PD patients is not fully understood. Information from several psychophysical, neurophysiological, and imaging studies has provided useful information on pain-processing mechanisms in PD that presents with and without pain. These studies, however, have yielded heterogenous results, probably because of methodological factors [1,2]. Quantitative sensory testing, the nociceptive withdrawal reflex to electrical stimuli, and scalp CO_2 laser-evoked potentials are commonly used to assess sensory and pain perception in PD patients. Augmented sensitivity to experimental pain and low sensitivity to somatic sensation in PD patients was demonstrated by reduced pain thresholds and increased sensory thresholds [3–6]. However, none of these assessments seem suitable to evaluate a change in the thresholds of any class of afferent fibers, despite the fact that quantitative analysis of each afferent class is essential to understand the underlying mechanisms of the pathological state and to evaluate the effect of analgesics.

The Neurometer®CPT (Neurotron, Baltimore, MD, USA) [7] is an apparatus that selectively measures the thresholds of three classes of afferent fibers by applying three different sinusoidal frequencies (2000 Hz, 250 Hz, and 5 Hz) at various intensities. The Neurometer®CPT is now widely used to evaluate peripheral nerve sensitization and dysfunction in various painful states, including neuropathic pain, or to evaluate the efficacy of analgesic drugs

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[8–10]. No neurodiagnostic measure besides the Neurometer®CPT can evaluate the full spectrum of sensory nerve function.

The use of the Neurometer®CPT in the present study makes it the first to evaluate pain and sensory sensitivity of each class of afferent fibers in PD patients. We also investigated the relationship of these thresholds with the presence or absence of pain, patients' use of L-dopa, and the severity of motor dysfunction. The therapeutic effects of dopaminergic medication were also evaluated to further understand pathological mechanisms underlying the pain and sensory dysfunction in PD.

2. Patients and methods

Patients with a clinical diagnosis of PD according to the criteria of the United Kingdom PD Society Brain Bank were recruited from the Department of Neurology of the Second Affiliated Hospital of Soochow University, China. Age- and sex-matched pain-free healthy controls were also recruited at our institution. Patients with dementia, depression, or concomitant disorders that might hamper sensory function were excluded. All patients were evaluated using the Unified PD Rating Scale (UPDRS) and the Hoehn and Yahr (H&Y) scale. Each patient was evaluated to confirm which side was most affected according to the UPDRS score.

This study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University. Each patient signed written consent before participation. PD patients were asked to describe any pain or sensory disturbances they were experiencing at the time of the study and that had already persisted for at least two months. The location of any pain was noted using the Brief Pain Inventory (BPI), and pain severity was recorded using the Visual Analog Scale (VAS). Pain and sensory disturbances were classified according to Ford's scheme [1]. The group of PD patients was divided into PD patients with pain (PDP) and PD patients without pain (PDNP). Medical conditions associated with or predisposing to painful symptoms, including diabetes, osteoporosis, rheumatic disease, arthritis, and disk herniation, were checked by examination and evaluation of patient clinical records.

Medication histories were noted with respect to L-dopa exposure and patients were subdivided into those with exposure to L-dopa (ELD) and those with no exposure to L-dopa (NLD). An approximation of the cumulative life-time amount of L-dopa was made based on the following equation: (daily amount of L-dopa (in mg) at 1 year after commencement) × 365 + [1/2] [maximum daily amount of L-dopa + daily amount of L-dopa at 1 year after commencement] × [interval (in years) from 1 year after commencement to reaching maximum dose × 365] + [1/2] [maximum daily amount of L-dopa + daily amount of L-dopa at death or discontinuation of L-dopa] × [interval (in years) from reaching maximum dose to death or L-dopa discontinuation × 365].

2.1. Apparatus and procedure

The Neurometer®CPT [7] was used to measure both current perception threshold (CPT) and pain tolerance thresholds (PTT). To selectively stimulate nerve fiber populations, the device applies transcutaneous sine-wave stimulation at 2000 Hz, 250 Hz, and 5 Hz at a current intensity of 0.01–9.9 mA via surface electrodes applied to the skin. The 2000 Hz frequency stimulates large Aβ fibers, the 250 Hz frequency activates Aδ fibers, and the 5 Hz frequency stimulates small C-polymodal fibers. Both CPT and PTT were measured on both the patients' middle fingers. The left and right fingers were tested separately in a random order across patients. During the first round of testing, PD patients were instructed to refrain from taking any dopaminergic medications the night before testing (referred to as "without medications" or "PDNM"). Patients were asked to take dopaminergic medications (equivalent to the first morning dose plus 100 mg of L-dopa) 1 h before the second round of testing (referred to as the "with medications" state or "PDM"). PTT was always tested last to minimize skin sensitization. Part III of the UPDRS, the clinician-scored monitored motor evaluation, was also assessed before and after dopaminergic medication.

To measure CPT, participants were asked to identify the presence or absence of the stimulus through a forced choice protocol. After an initial tentative threshold was determined, we administered stimuli that varied near the presumed threshold to confirm the consistency and reproducibility of the threshold measurement. The threshold of perception was the measured response.

To measure PTT, participants self-administered the electrical stimuli, which increased in intensity through a series of predetermined levels. The test started when participants held down the test button. When the stimulus became "intolerable pain", the participant released the test button to stop the test; the intensity at this point was recorded as the PTT.

2.2. Statistical analysis

The data were analyzed with the SPSS package version 17 (SPSS Inc., Chicago, IL, USA) and the results were expressed as means and standard deviations. Differences in age and gender distributions between the two groups were assessed using independent Student's t-tests and χ^2 tests. A two-way ANOVA was used to assess the differences in CPT or PTT obtained at each frequency, with side (the more- and less-affected sides) as the within-subjects factor and status group (like PDP, PDNP, or controls) as the between-subjects factor. Various ANCOVAs were used for each independent variable and post-hoc comparisons were made with the Bonferroni test. The statistical analysis was performed at a 95% confidence level and a P-value less than 0.05 was typically considered statistically significant. However, because three groups were included, the P-values were corrected post-hoc with the Bonferroni test and P-values less than 0.015 were considered to meet the threshold for significance.

3. Results

3.1. Subject characteristics

Demographic and clinical characteristics of the study population are presented in Table 1. This study was performed using 72 PD patients and 35 age- and sex-matched controls. Thirty patients (41.7%) reported having experienced significant pain or sensory disturbances that had lasted two months or more. Complaints consisted mostly of musculoskeletal pain (seven in the neck and shoulder, 10 in the lower back, and eight in the lower extremities) and also included three instances of peripheral neuropathic pain (ischioneuralgia) and two of central neuropathic pain (a burning sensation present all over the body). The PD subgroups did not differ significantly with respect to age, gender, disease duration, or L-dopa equivalent dose ($P > 0.05$), but differences in the UPDRS motor score and H&Y stage were observed ($P < 0.05$). PD patients with pain exhibited more severe UPDRS motor scores and more advanced H&Y stages than did PD patients without pain.

3.2. Pain and sensory sensitivity in PD patients and controls

Significant differences in CPT were evident between groups but not between sides at 2000 Hz, 250 Hz, and 5 Hz, and in PTT at 2000 Hz and 250 Hz. PTT at 5 Hz did not differ between groups or between sides (Table 2). Post-hoc analyses revealed CPT to be significantly higher at all frequencies and PTT to be significantly lower at 2000 Hz and 250 Hz in PD patients with pain than in healthy controls. CPT was significantly higher at 2000 Hz and 250 Hz and PTT was significantly lower at 2000 Hz and 250 Hz in PD patients without pain than in healthy controls. PD patients with pain had higher CPT at 5 Hz and 250 Hz than PD patients without pain (Table 2).

3.3. The relationship of PD severity to pain and sensory thresholds

The H&Y stage did not correlate with CPT or PTT, while the UPDRS motor score exhibited a significant positive correlation with

Table 1
Demographic and clinical characteristics of the study population.

	CTRL (n = 35)	PD (n = 72)	PDNP (n = 42)	PDP (n = 30)	P
Gender (M/F)	19/16	44/28	28/14	16/14	0.076[a] 0.259[b]
Age (yrs)	65.9 ± 8.9	64.8 ± 8.8	65.9 ± 8.9	63.2 ± 8.4	0.518[a] 0.203[b]
Disease duration (yrs)	–	4.9 ± 3.1	4.4 ± 2.9	5.6 ± 3.2	0.119[b]
H&Y stage (1–5)	–	2.0 ± 0.7	1.9 ± 0.7	2.3 ± 0.6	0.007[b]
UPDRS III	–	29.5 ± 13.4	25.6 ± 12.9	35.1 ± 12.3	0.002[b]
LEDD, mg	–	362.7 ± 273.2	330.3 ± 285.4	402.3 ± 258.2	0.279[b]

CTRL, healthy controls; PD, patients with Parkinson's disease; PDP, PD patients with clinical pain; PDNP, PD patients without clinical pain; UPDRS III, Unified Parkinson's Disease Rating Scale, part III (motor assessment); H&Y, Hoehn and Yahr; LEDD, L-dopa equivalent daily dose.

[a] CTRL - PD comparison.

[b] PDNP - PDP comparison.