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Impaired pain processing in Parkinson's disease and its relative association with the sense of smell

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ABSTRACT

Background and purpose: Many non-motor symptoms are associated with Parkinson's disease (PD). Of these, pain and olfactory disturbance tend to be common premotor symptoms. PD has been shown to exhibit abnormal central pain processing, although underlying mechanisms are not yet fully understood. In order to investigate this further, we assessed PD patients by specific Aδ stimulation with intra-epidermal needle electrode and determined olfactory function.

Methods: Forty-two patients (18 males and 24 females) with PD and 17 healthy control subjects (8 males and 9 females) were studied. A thin needle electrode was used to stimulate epidermal Aδ fibers, and somatosensory evoked potentials (SEPs) recorded at the vertex. Olfactory function was evaluated using the Odor Stick Identification Test for Japanese (OSIT-J) and its relationship with pain-related SEPs was investigated.

Results: There were no significant differences in N1 latencies or P1 latencies although N1/P1 peak-to-peak amplitudes were significantly lower ($p < 0.01$) in PD patients than in control subjects. In PD patients, there were significant correlations between N1/P1 amplitudes and disease duration ($r = -0.35$, $p < 0.05$), Hoehn-Yahr stage ($r = -0.38$, $p < 0.05$) and UPDRS part III ($r = -0.42$, $p < 0.01$). Furthermore, the OSIT-J scores correlated with SEP amplitude ($r = 0.41$, $p < 0.01$).

Conclusion: Pain processing in PD patients was impaired under specific nociceptive stimulation of Aδ fibers and significant correlation with smell dysfunction was detected. We suggest that this mechanism may involve the limbic system during PD pathology.

1. Introduction

Pain is an important and distressing symptom in Parkinson's disease (PD) [1]. However, the specific features of this phenomenon and the mechanisms involved have not yet been fully assessed. While several studies have investigated pain threshold with mechanical heat or cold stimulation in PD patients, such results remain controversial [2–4]. In general, it is difficult to evaluate the degree of pain objectively, while pain-related somatosensory evoked potentials (SEPs) have been considered to be one of the reliable objective assessments of pain processing [5,6].

Pain-related SEPs may be recorded by laser, heat, electric, and mechanical stimulations [7]. Each stimulus to activate the specific nociceptive receptor system in the skin may evoke specific central pain processing, though the precise features are not well understood. Recently, Inui et al. recorded evoked potentials induced by epidermal electrical stimulation (ES) using a thin needle electrode, which can specifically activate the Aδ fiber-mediated pain mechanism [5]. The authors of this magnetoencephalography (MEG) study subsequently reported that the vertex biphasic SEP component corresponded approximately to the activity of medial temporal cortex [8]. ES with this particular needle electrode is a convenient method for the selective stimulation of Aδ fibers, since it represents a very simple technique which does not require any special apparatus.

In the present study, we recorded pain-related SEPs by using ES methodology to activate Aδ mediated pain mechanisms in PD patients and healthy controls. Furthermore, pain symptoms antedate the onset of motor symptoms in some PD patients [9,10]. Olfactory dysfunction is also recognized as non-motor symptom in PD patients [11–13] and is considered as a useful diagnostic marker of preclinical PD because pathological changes of the olfactory systems begin before motor symptoms develop [14]. Furthermore,

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in a recent positron emission tomography study, Baba et al reported that odor-identification performance was closely associated with broad cortical dysfunction of the piriform cortex and amygdala, and suggested that cognitive deficit in olfactory perception is an important aspect of hyposmia in PD and that this deficit is caused by altered brain metabolism in the amygdala and piriform cortex [15]. Consequently, we considered that pain processing impairment may be correlated to olfactory dysfunction in similar regions, and investigated whether there may be an association between pain-related SEPs and olfactory function.

2. Methods

2.1. Subjects

Forty-two patients (18 males and 24 females) with PD and 17 healthy control subjects (8 males and 9 females) were studied. Patients were recruited from the Nagoya University Hospital, Japan. Patients with PD fulfilled the diagnostic criteria for PD [16]. Motor performance was assessed using the Hoehn and Yahr (H&Y) scale and the Unified Parkinson's Disease Rating Scale (UPDRS) part III-motor examination. Using item 17 from the UPDRS part II-activities of daily living, PD patients were classified as 'with pain' (point 1–4) or 'without pain' (point 0) groups. Patients with symptoms and signs compatible with an atypical parkinsonian syndrome were excluded. Exclusion criteria included clinical findings or nerve conduction evidence of peripheral neuropathy or of any other disease potentially causing sensory impairment. Components of ES related SEPs are known to be changed by cognitive function. Consequently, patients with cognitive defects (Mini-Mental State Examination score below 25/30), or taking analgesics or antidepressant treatment, were also excluded. Each patient's daily intake of anti-parkinsonian medications (e.g., levodopa, dopamine agonist, monoamine oxidase type B inhibitor, catechol-O-methyl transferase and amantadine) was recorded. The total daily levodopa equivalent dose was calculated for each patient according to published conversion formulas [17]. All PD patients were examined in the on condition.

The Ethics Committee of Nagoya University School of Medicine approved all aspects of this study. Written informed consent for participation was obtained from all subjects.

2.2. Preferential stimulation of Aδ fibers by intra-epidermal needle electrode

We recorded pain-related SEPs using methodology described previously [5] and a custom-made needle electrode (Nihon-Koden Co. Ltd. Tokyo, Japan). Electrical stimulus was a current constant square wave pulse delivered at random intervals between 0.1 Hz. Stimulus duration was 1.0 ms. Current intensity was at a predetermined level which produced a definite pain sensation in each subject. We stimulated the face, upon the cheek, approximately 3 cm below the infra-orbital margin. Stimuli were applied in PD patients to the dominant side of motor symptoms, and was applied consistently to the right side of control subjects. Stimulation produced a well-defined pricking pain without definite tactile sensations. Stimulus intensity was under 0.4 mA which does not induce other pain receptors.

2.3. Recording of SEPs

An exploring electrode was placed at the Cz (vertex) according to the 10-20 International system. The reference electrode was applied to the left earlobe. We focused upon evoked potential responses recorded from the Cz. Impedance for all electrodes remained under 5 kΩ. Responses were recorded with a 0.5–50 Hz bandpass filter at a sampling rate of 1024 Hz. Analysis time was 1 s following stimulation. In each stimulus condition, ten responses with approximately 10 s randomized stimulation intervals were collected and averaged in one trial. In addition, three trials were recorded over 2 min intervals in order to avoid habituation. During SEP recording, the subjects laid on a bed in a warm and quiet room. SEP components were identified on the basis of their latency and polarity and were labeled in accordance with a previous report [6]. Peak-to-peak amplitude was measured for the vertex biphasic SEP component (N1/P1). Since the number of detectable SEPs in PD is low, and in order to allow comparison with other diseases, we defined non-recordable SEPs as having an amplitude of zero.

Epochs in which signal variations were larger than 80 μV in the EEG were excluded from data analysis. After ensuring that our methodology was consistent and produced reproducible data, we conducted three trials which were then averaged for analysis.

2.4. Olfactory testing

The odor-identification performance of each subject was measured using the Odor Stick Identification Test for Japanese (OSIT-J, Daiichi Yakuhin, Co., Ltd., Tokyo, Japan), which consists of 12 odorants familiar to Japanese people. This test has been successfully applied for the assessment of odor-identification ability in Japanese PD patients and the precise protocol used has been described previously [18].

2.5. Statistical analysis

We calculated the mean and the standard deviation (SD) of all variables for all patients and control subjects. The difference of age between PD patients and controls was determined with the student *t*-test. We used the χ^2 test to compare sex distribution among groups. Stimulus intensity and parameters associated with pain-related SEPs between group differences were analyzed using analysis of variance. Spearman's rank correlation was used to examine correlations between various parameters of pain-related SEPs and H&Y scale, UPDRS part III, and OSIT-J score, and stimulus intensity. Differences in pain-related SEP parameters between PD patients with and without pain were determined using the Kruskal–Wallis test. Statistical computing was performed with JMP software, version 7. A value of $p < 0.05$ was considered to define statistical significance.

3. Results

3.1. Clinical characteristics

The age of PD patients (66.7 ± 6.9 years) and controls (63.7 ± 6.4 years) were not significantly different. Similarly, there was no significant difference identified in gender between PD patients and controls. The mean disease duration of PD was 6.5 ± 5.1 years. In PD patients, H&Y stage was 2.3 ± 1.1, and UPDRS part III was 21.6 ± 10.7. Total daily levodopa equivalent dose was 343 ± 331 mg. Twenty one of the 42 PD patients reported to be experiencing pain; OSIT-J score was 4.9 ± 3.2, compared to 8.9 ± 2.3 in control subjects, which was significantly lower ($p < 0.01$).

3.2. Pain-related SEP recordings

SEPs were not evoked in six PD patients. Stimulus intensities were not significantly different between PD patients and controls. Furthermore, stimulus intensities did not differ in PD patients with or without detectable SEPs. There were no significant differences in N1 or P1 latencies between PD patients (N1: 188.7 ± 39.5 ms, P1: 265.8 ± 46.2 ms) and controls (N1: 183.5 ± 42.1 ms, P1: 255.5 ± 53.0 ms). However, N1/P1 amplitudes were significantly lower in PD patients (9.0 ± 5.8 μV) than in controls (13.7 ± 6.4 μV)

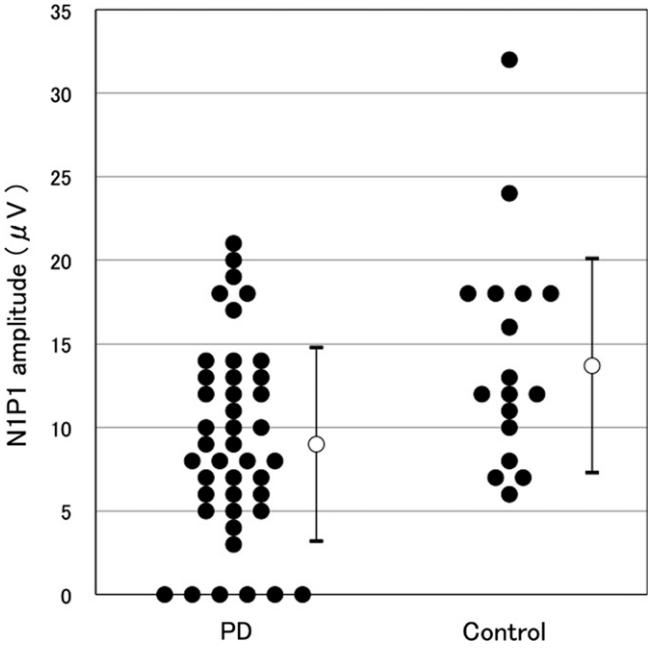

Fig. 1. Comparison of N1/P1 amplitude between PD patients ($N = 42$) and control subjects ($N = 17$). Symbols to the right of each group represent mean ± SDs.