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Cognitive functions in Parkinson's disease: Relation to disease severity and hallucination

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ABSTRACT

Objective: We wished to relate severity of Parkinson's disease (PD) with cognitive function in relation to cerebral blood flow (CBF).
Methods: Eighty-one consecutive PD patients were enrolled in this study. We used Mini-Mental State Examination (MMSE) and Wechsler Adult Intelligence Scale-Third edition (WAIS-III) to evaluate cognitive functions, and three-dimensional stereotactic ROI template (3DSRT) and Statistical Parametric Mapping (SPM) 8 to evaluate single photon emission CT (SPECT) recordings of regional CBF.
Results: The mean MMSE score of PD patients was 27.4 ± 2.4. The scores of most patients were higher than 23/30. On the other hand, the mean Full-scale IQ of PD patients was 88.4 ± 17.3 in WAIS-III, which was lower than that of normal controls. In particular, visuospatial function score of most patients was lower. There was significant correlation between cognitive scores and Hoehn & Yahr stage and hallucinatory episodes. PD Patients with stage III and IV showed significant deterioration in cognitive functions compared to stage II patients. Analysis of CBF revealed relative reductions in perfusion in the cerebral cortex relative to that in normal control. SPM 8 showed that cognitive functions in PD patients were positively correlated with rCBF in the thalamus and cingulate gyrus.
Conclusions: This is the study to demonstrate the cognitive impairments in PD patients using WAIS-III. Visuospatial dysfunction might be caused by decrease in rCBF in the parietal and occipital lobes and dorsolateral prefrontal cortex. The severity of cognitive impairments in PD patients was correlated with disease severity and hallucinatory episodes.

1. Introduction

Cognitive impairments are one of the most common non-motor symptoms in patients with Parkinson's disease (PD). Subtle cognitive impairments that usually progress to more severe cognitive impairments and dementia may exist from the initial stage of PD. Cognitive impairments may be ascribed to dopaminergic depletion and failure of the fronto-striatal basal ganglia circuits [1]. Patients with PD have a four- to six-fold increase in the risk of developing dementia compared to the age-matched general population [2]. In a follow-up study, the prevalence of PD with dementia (PDD) was 20% at 5 years after the onset, and increased to 45% at 15 years and 83% at 20 years [3]. Since the mortality is higher in patients with PDD than in non-demented patients [4], the evaluation of cognitive functions in patients with PD is very important.

In the present study, we evaluated the cognitive functions in patients with PD and examined the correlation between cognitive functions and patient-related factors, motor symptoms, and mood states. Additionally, the regional cerebral blood flow (rCBF) in patients with PD was assessed in terms of the results of cognitive functions. We hypothesized that rCBF in patients with PD may be lower than that of normal controls and that the results of cognitive functions and rCBF may be correlated.

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2. Methods

2.1. Patients

The subjects were 81 patients with PD that visited our institute between July 2008 and November 2011. Disease severity of patients with PD in this study was determined by Hoehn & Yahr (H&Y) stage. Hallucinations, ADL, and motor symptoms were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS). Mood states were evaluated by a profile of mood states (POMS) [5]. The mean age of patients was 62.8 ± 7.4 years. Mean disease duration was 11.9 ± 5.4 years. Levodopa equivalent daily dosage (LEDD) was 966.5 ± 390.7 mg. The mean H&Y stage score in the drug-on condition was 2.8 ± 0.7. When we classified patients with PD according to H&Y stage, there were 32 stage II patients, 38 stage III patients, and 11 stage IV patients. In the evaluation of UPDRS, the hallucinations score was 0.4 ± 0.5; the ADL score was 7.8 ± 6.3; the motor score was 13.1 ± 10.4; the tremor score was 0.5 ± 1.1; the rigidity score was 2.5 ± 2.8; the akinesia score was 3.8 ± 4.3; and the postural instability score was 3.0 ± 2.5. In the evaluation of POMS, the *Tension–Anxiety* score was 51.5 ± 9.1; the *Depression* score was 50.1 ± 9.4; the *Anger–Hostility* score was 44.3 ± 7.7; the *Vigor* score was 40.1 ± 8.2; the *Fatigue* score was 47.9 ± 8.4; and the *Confusion* score was 56.7 ± 10.6.

Written informed consent was obtained from every patient before the study. The ethical committee of Okayama University Hospital has approved the use of human subjects for this study.

2.2. Evaluation of cognitive functions

All patients with PD were assessed using the Mini-Mental State Examination (MMSE) and the Wechsler Adult Intelligence Scale-Third edition (WAIS-III). Trained clinical psychologists and speech therapists conducted the neuropsychological tests for all patients. Neuropsychological tests were performed for patients with drug-on condition. When we evaluated the cognitive functions of patients with PD with motor fluctuation, we performed neuropsychological tests for patients with the drug-on condition as judged by the patient's self-report. We stopped the tests when patients with PD presented with motor fluctuations.

Twelve subtests in WAIS-III were conducted for patients with PD in this study. We excluded *Object assembly* and *Symbol search* in order to reduce patient fatigue. In accordance with the protocol for WAIS-III, raw scores were converted to age-corrected scaled scores in the normal control group, which consists of 1381 healthy adult Japanese selected randomly [6]. The mean IQ of normal control in WAIS-III is set from 90 to 109 [6]. WAIS-III scores are shown as comparison of IQ with scores of normal control [6]. Next, we calculated the summary scores of Full-scale IQ (FIQ), Verbal IQ (VIQ), and Performance IQ (PIQ), and group indexes for Verbal Comprehension (VC), Working Memory (WM), and Perceptual Organization (PO).

2.3. rCBF study

Single-photon emission computed tomography (SPECT) was performed as reported previously [7]. All patients with PD received ^{99m}Tc ethyl cysteinate dimer SPECT (Fujifilm RI Pharmaceuticals Ltd., Tokyo, Japan). SPECT was performed for patients with the drug-on condition. We used the Patlak plot method to quantify the rCBF in patients with PD [8]. After all patients underwent SPECT, we evaluated rCBF by using the three-dimensional stereotactic ROI template (3DSRT) and Statistical Parametric Mapping (SPM) 8 (Department of Cognitive Neurology, UCL, London, UK).

3DSRT is a fully automated rCBF quantification program with 636 regions of interest (ROIs) in total [9]. We quantified the blood flow in each ROI as the value in milliliters per 100 g/min and showed it in 12 segments: callosomarginal, precentral, central, parietal, angular, temporal, occipital, pericallosal regions, lenticular nucleus, thalamus, hippocampus, and cerebellum. The 3DSRT values of patients with PD are compared to the normal control in these segments (rCBF of PD patient's/rCBF of normal control × 100 [%]). We used the scores of normal control of healthy adult Japanese in 3DSRT research shown in a previous study by Matsuda [10].

The correlation between cognitive functions and rCBF was analyzed using SPM 8 [11]. All SPM calculations were performed using Matlab version 2012a (MathWorks, Sherborn, Massachusetts, USA). The SPECT images were spatially normalized to the standardized brain template [12]. The normalized images were smoothed to account for variations in subtle anatomic structures [13]. Statistical correlation between cognitive functions and rCBF was explored voxel by voxel by setting each patient's IQ as a covariate of interest. Significance was accepted if the clusters survived a corrected threshold of $p < 0.05$. We showed anatomical regions with correlation between cognitive functions and rCBF using Talairach Daemon software [14].

2.4. Statistical analysis

First, all data are shown as mean ± standard deviation (SD) in MMSE and WAIS-III. Second, we used a two-tailed Pearson's correlation coefficient test between cognitive functions (MMSE, WAIS-III) and patient-related factors (age, disease duration, LEDD, hallucinations), motor symptoms (H&Y stage and UPDRS), and mood states (POMS). We conducted Bonferroni corrections for multi-factor analyses in UPDRS items. Finally, we focused on the H&Y stage that was most strongly correlated with cognitive functions. We conducted a one-way analysis of variance (ANOVA) to assess the significance of mean differences in demographic data and the results of cognitive functions in three groups (II, III, and IV) classified by H&Y stage and then performed a post hoc Bonferroni test. All statistical analyses were performed with SPSS 15.0 for Windows. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Cognitive functions in patients with PD

The mean MMSE score of patients with PD was 27.4 ± 2.4 (range: 21–30). Five patients (6.1%) were under the cut-off point, that is, 23/30. The scores of most patients were more than 23/30 in MMSE.

The mean FIQ of patients with PD was 88.4 ± 17.3 (range: 57–125) in WAIS-III (Supplementary Table 1). The mean FIQ was lower than that of normal controls. The VIQ and PIQ were 92.9 ± 16.4 (range: 65–129) and 85.2 ± 17.4 (range: 53–120), respectively. The VIQ was within the normal range; however, the PIQ was lower than that of normal controls. In the group index, the VC index was 93.7 ± 15.9 (range: 65–129). The WM index was 93.1 ± 13.3 (range: 60–130). The VC and WM indexes were within the normal range. The PO index was 88.2 ± 17.7 (range: 52–125). The PO index was lower than that of normal controls. All verbal subtest scores of patients with PD were within the normal range. The *Block design*, *Picture arrangement*, and *Digit symbol cording* scores were lower than those of normal controls.