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Analysis among cognitive profiles and gray matter volume in newly diagnosed Parkinson's disease with mild cognitive impairment

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ABSTRACT

Purpose: To analyze the characteristics of neuropsychological profiles and gray matter volume in de novo, drug-naïve Parkinson's disease with mild cognitive impairment (PD-MCI).
Methods: Fifty-two newly diagnosed PD patients were assessed with neuropsychological testing, and PD-MCI was defined in patients with at least one or more abnormal cognitive test domains. PD with normal cognition (PD-NC) did not meet the criteria for PD-MCI or PD with dementia. Brain MRI scans was acquired from the patients and healthy controls (HC). The imaging processing and analysis of the gray matter (GM) volume were performed platform to determine the difference between PD-MCI and PD-NC.
Results: There were no differences of motor subscores between PD-MCI and PD-NC. The clinical dementia rating, global deterioration scale, and verbal memory were significantly worse in PD-MCI than in PD-NC. GM volume loss was observed in the right hippocampus, right cuneus, and right precuneus in PD-NC compared to in the HC. PD-MCI had significantly decreased GM volume in the bilateral temporal and frontal areas compared with that of the HC. The GM volume was significantly decreased in the right temporal pole, left precuneus, medial frontal and posterior cingulated gyrus in PD-MCI compared with PD-NC.
Conclusions: Clinical dementia ratings and global deterioration scales could differentiate PD-MCI from PD-NC. Verbal memory impairment is characterized as a cognitive deficit of de novo PD-MCI and is associated with the posterior cortical area.

1. Introduction

Mild cognitive impairment (MCI) is common in Parkinson's disease (PD), even in newly diagnosed PD patients without medication [1–3]. The patients with early, untreated PD showed a twofold increase in the proportion of cognitive impairment compared to the controls [2]. A number of PD with MCI (PD-MCI) patients develop dementia earlier than do those who are not cognitively impaired [4]. Early identification of PD-MCI could be important for the early detection of PD patients at risk for dementia.

The executive dysfunction in PD involving manipulation of information within the working memory that is representative of the cognitive deficiency of early PD results from damage to the basal ganglia (BG) and/or frontal cortex [5–11] or dysfunction of the fronto-striatal dopaminergic network [6,12–14].

Recently, gray matter (GM) atrophy in PD-MCI has been shown in the temporal, parietal and frontal cortices as well as in the bilateral caudal hippocampus, amygdala and right putamen [15]. GM loss in PD is correlated with the global cognitive score and not with motor impairment in most of these regions [15].

We analyzed the characteristics of neuropsychological profiles and gray matter volume in newly diagnosed PD-MCI compared with PD with normal cognition (PD-NC).

2. Methods

2.1. Patients

Fifty-two PD patients who were newly diagnosed according to the UK Brain Bank clinical criteria were enrolled in the study [16]. The patients had no dopaminergic agent medication history. The patients were evaluated with the Seoul Neuropsychological Screening Battery (SNSB) [17] to determine PD-MCI by established diagnostic criteria

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[4]. In addition, PD-MCI patients should not show evidence of abnormality in the activities of daily living (ADL) [17]. The SNSB is a neuropsychological test (NPT) set, which covered the following cognitive subsets [18]: attention (the forward and backward digit span and letter-cancelation tests); language functions (the Korean version of the Boston Naming Test [K-BNT] [19] and calculation); visuospatial function (the Rey Complex Figure Test [RCFT]); verbal memory (the Seoul Verbal Learning Test [SVLT]); visual memory (the RCFT, immediate recall, 20-minute delayed recall, and recognition); and frontal executive function (motor impersistence, contrasting program, go-no-go test, fist-edge-palm, alternating hand movement, alternating square and triangle, Luria loop, phonemic and semantic Controlled Oral Word Association Test [COWAT], and Stroop test). We considered the attention function to be abnormal if at least 2 of the 3 items were abnormal. Abnormal language, memory and visuospatial function were defined by a score below the 16th percentile of the norm. The frontal/executive function tests were classified into 3 groups as follows: the motor executive function, the COWAT, and the Stroop test. The frontal/executive function was considered to be abnormal when at least 2 of the 3 tests were abnormal. Based on these criteria, PD-MCI was defined as SNSB showing at least one or more abnormal cognitive domains. All the patients were assessed with the Korean version of the Mini-Mental State Examination (K-MMSE) [21], the clinical dementia rating (CDR) scale [22], the global deterioration scale (GDS) [23], the Korean version of the Montreal cognitive assessment (MoCA-K) [24], and the frontal assessment battery (FAB) [25]. The Parkinsonian motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS). Based on the UPDRS motor scores, the motor subtypes were categorized in 3 groups as follows: akinetic-rigid type (ART), mixed type (MT), and tremor-dominant type (TDT) [26]. The motor symptoms were categorized by 5 subscores (tremor, rigidity, bradykinesia, postural instability and gait disturbance [PIGD], bulbar dysfunction) that were calculated according to the established literature [5]. All of the PD patients were evaluated with the Hoehn–Yahr (H–Y) scale. The exclusion criteria included evidence of focal brain lesions, diffuse white matter hyperintensities, or multiple lacunes in the BG by MRI examinations. In the cases in which clinical signs were observed that satisfied the criteria of possible atypical, secondary, or iatrogenic Parkinsonism and dementia, the patients were excluded. Possible medical comorbidities were excluded by laboratory tests, including the thyroid function test, vitamin B12 and folic acid levels, and VDRL test. Twenty-two healthy volunteers were used as controls for the voxel-based morphometry (VBM) analysis (10 male, 12 female, age = 61.9 ± 7.9). The PD-NC did not meet the criteria for PD-MCI or PDD [4,27]. The healthy controls (HC) had no active neurological disorders and no cognitive complaints. The protocol was approved by the Institutional Review Board of Busan Paik Hospital. We obtained written informed consent from all the subjects participating in this study.

2.2. MRI acquisition

The scans of the healthy controls and patients were acquired using a Philips 3.0-T scanner (Philips Achieva; Philips Medical System, Best, the Netherlands) with a head coil. Head motion was minimized with restraining foam pads provided by the manufacturer. A high resolution T1-weighted MRI volume dataset was obtained from all the subjects using a 3-dimensional T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 256 matrix; a 256 × 256 reconstructed matrix with 182 slices; a 220 mm field of view; 0.98 × 0.98 × 1.2 mm^3 voxels; echo time 4.6 msec; repetition time 9.6 msec; flip angle 8° and slice gap 0 mm. To accelerate the data acquisition, SENSE (Sensitivity Encoding) parallel imaging with an acceleration factor of 2 was applied.

2.3. VBM of gray matter

The imaging processing and analysis were performed using the SPM8 (Statistical Parametric Mapping 8, UK, http://www.fil.ion.ucl.ac.uk/spm) on the Matlab (The Mathworks, Natick, MA, USA) platform. For the VBM pre-processing, the VBM8 toolbox, which is one of the SPM8 extension toolboxes, was utilized in the standard manner with the following steps: the segmentation procedure using the prior tissue probability map and Gaussian mixture model, the normalization procedure registering the MNI template (Montreal Neurological Institute, Montreal, Canada), the modulation procedure for intensity compensation using Jacobian determination, and the smoothing procedure applied to a Gaussian kernel of 6-mm full-width half maximum (FWHM). For the volumetric analysis, one-way ANOVA was conducted using the GLM (General Linear Model) to identify the entire brain volume with significant differences between PD-NC, PD-MCI, and the healthy controls. We did not perform multiple-comparison correction methods because multiple-comparison correction methods would inevitably adjust for statistical error but not for biological effect [28]. We had to consider the biological relevance and did not correct for multiple comparisons when performing SPM analyses. In addition, multiple-comparison correction could reduce the statistical power. The age and total intracranial volume (TIV) were entered as the covariates, and the statistical significance was set to $p < 0.001$ with uncorrected multiple comparisons.

2.4. Statistical analysis

The statistical comparison of the parametric clinical items between PD-MCI and PD-NC patients was performed with the t and χ^2 test for the categorical and continuous variables, respectively. The nonparametric data were analyzed by the Wilcoxon rank sum and Fisher's exact test for the categorical and continuous variables, respectively. The statistical analyses were performed using commercially available software (SPSS, version 19.0). The scores of various neuropsychological tests were adjusted for age and education, and $p < 0.05$ was considered statistically significant.

3. Results

There were no significant differences in the sex, age, age at onset, disease duration, education, UPDRS motor scores, H–Y stage, motor

Table 1
Demographics, clinical characteristics, subtype and motor symptoms of 52 newly diagnosed PD patients with mild cognitive impairment and normal cognition.

	PD-MCI (24)	PD-NC (28)	p-Value
Demographics & clinical characteristics			
Sex (male)†	14 (58.3)	12 (42.8)	0.785
Age (y)	67.2 ± 7.4	67.9 ± 10.1	0.852
Age at onset (y)	65.1 ± 8.9	66.3 ± 9.8	0.476
Disease duration (m)	25.7 ± 49.2	19.2 ± 19.1	0.970
Education (y)	8.9 ± 4.0	7.0 ± 4.0	0.240
UPDRS III	20.3 ± 9.5	17.2 ± 8.0	0.273
Hoehn and Yahr stage	2.25 ± 0.51	2.33 ± 0.62	0.667
Subtype & motor symptoms			
Subtype†			0.060
Akinetic-rigid type	9 (37.5)	9 (50.0)	
Mixed type	12 (50.0)	3 (16.7)	
Tremor-dominant type	3 (12.5)	6 (33.3)	
Subscore			
Tremor	2.3 ± 1.9	1.8 ± 1.4	0.354
Rigidity	4.6 ± 2.8	3.8 ± 2.6	0.323
Bradykinesia	6.5 ± 3.3	5.5 ± 3.2	0.318
PIGD	2.5 ± 2.0	2.4 ± 1.9	0.969
Bulbar dysfunctions	2.0 ± 1.1	1.5 ± 1.2	0.120

*Mean ± SD; †frequency (%); Parkinson's disease patients with mild cognitive impairment, PD-MCI; Parkinson's disease patients with normal cognition, PD-NC; United Parkinson's Disease Rating Scale, UPDRS; postural instability and gait disturbance, PIGD.