Structural Changes on the Brain MRI and Cognitive Function in Parkinson Disease

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Abstract: *Purpose*: Cognitive impairment in Parkinson disease (PD) related with the fronto-striatal dysfunction as one cause of subcortical dementia. However, cognitive impairment in PD might be associated with medial temporal lobe atrophy in recent studies. We carried out this study to know whether structural changes on brain MRI are responsible for cognitive dysfunction in PD.

Materials and Methods: We recruited 183 patients who were newly diagnosed with PD from January, 2007 to February, 2012. All patients were undertaken brain MRI and neuropsychological assessment. Structural changes of the brain images were evaluated with visual rating scales. We analyzed clinical and neuro-imaging data to assess a relation between cognitive function and brain structural changes in the total patients and did subanalysis with PD-cognitively declined (PD-CD) and PD-cognitively preserved (PD-CP) subgroup.

Results: Total scores of the MMSE and 3MS was worsened as havingsevere white matter change (WMC), ventricular enlargement (VE), medial temporal lobe atrophy (MTA), and cortical atrophy in PD patients. PD-CD showed more severe WMC, VE and MTA than those in PD-CP patients even after adjustment of age and durations of education. Degree of the MTA among the brain structural changes was the most relevant factor for cognitive dysfunction in PD patients.

Conclusions: Although cognitive dysfunction in PD is suggestive of subcortical origin, medial temporal structure also may have an important role for cognition in PD. Therefore, clinicians need thorough evaluation of the structural changes in the brain MRI as well as neuropsychological assessment to define cognitive function in PD.

Keywords: Parkinson disease, dementia, cognitive function, brain magnetic resonance imaging, atrophy.

INTRODUCTION

Parkinson disease (PD) is the second common disease among neurodegenerative disorders. PD is characterized by resting tremor, rigidity, bradykinesia, and postural instability which are caused by the loss of dopaminergic cell in the midbrain. In addition to motor symptoms, non-motor symptoms such as cognitive decline, sleep disorder and depression are common in PD and those have been getting more attention recently.

The risk of dementia of PD is 2-6 folds higher than the average elderly and it could be presented even in the early stage of PD [1, 2]. PD with dementia showed a higher risk of falls, injuries and complication like traumatic hemorrhage than those without dementia. Ultimately they had reduced capacity of independent living. It could increase burden of their families [3, 4]. So, it is important to have concern and evaluate cognitive function routinely in PD patients.

Cognitive decline in PD had been thought to be dysfunction of fronto-subcortical circuit [5, 6]. However, recent studies revealed that many other factors such as accumulation of cortical Lewy body, amyloid plaque, and neurofibrillary tangles and deficiency of choline are associated with PDD [7-9]. The relations of cognitive decline in PD and brain structural lesion had suggested from some neuroimaging studies. Cerebral white matter change (WMC) related to the cholinergic pathway is more severe in PDD than PD without dementia [8, 10]. As having severe cortical atrophy (CA) of the inferior parietal lobe and the orbito frontal lobe, there was more severe cognitive decline in the early stage of PD [9]. And other study suggested that hippocampal atrophy and lateral ventricular enlargement could be used as a biomarker of cognitive function in PD. Otherwise, there were other studies showed opposite results like do not have correlation, significantly [11, 12]. There were no consistent results about the correlation of structural change with cognition in PD patients.

Therefore, we studied about the possible roles of the brain structural changes such as WMC, ventricular enlargement (VE), medialtemporal lobe atrophy (MTA), and CA to the cognitive decline in PD with numerous patients.

MATERIALS AND METHODS

1. Subjects

We recruited 183 patients from the memory clinic at Chungnam National University Hospital who were

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newly diagnosed with PD from January, 2007 to February, 2012, retrospectively. 58 patients were excluded because alternative diagnosis was given during following-up and20 patients who had missing data for the study were excluded, also. Conclusively, we included 105 PD patients who were suitable for the study.

We reviewed medical records of the patients to get the information about age, gender, durations of education, vascular risk factors (diabetes mellitus and hypertension), laboratory test results and clinical features of PD.

We analyzed two types of subgroups with these patients. At first, we classified the patients into 3subgroupsaccording to their motor symptoms of the PD using Hoehn and Yahr (H&Y) stage [13] like group of stage 1, group of stage 2 and group of stage 3 or 4. In our study, there was no one who was in H&Y stage 5. Maybe patients of that stage had lied down at home or nursing home and got already diagnosis before. Second, we divided the patients into 2 subgroups by score of the Mini-Mental State Examination (MMSE) [14]: PD-cognitively decline group (PD-CD) (MMSE<24) *vs.* PD-cognitively preserve group (PD-CP) (MMSE≥24) to compare the structural changes of the brain and cognitive function.

2. Methods

We conducted the Korean version of modified Mini-Mental State (3MS) examination [15] and MMSE to assess the general level of cognitive function for total

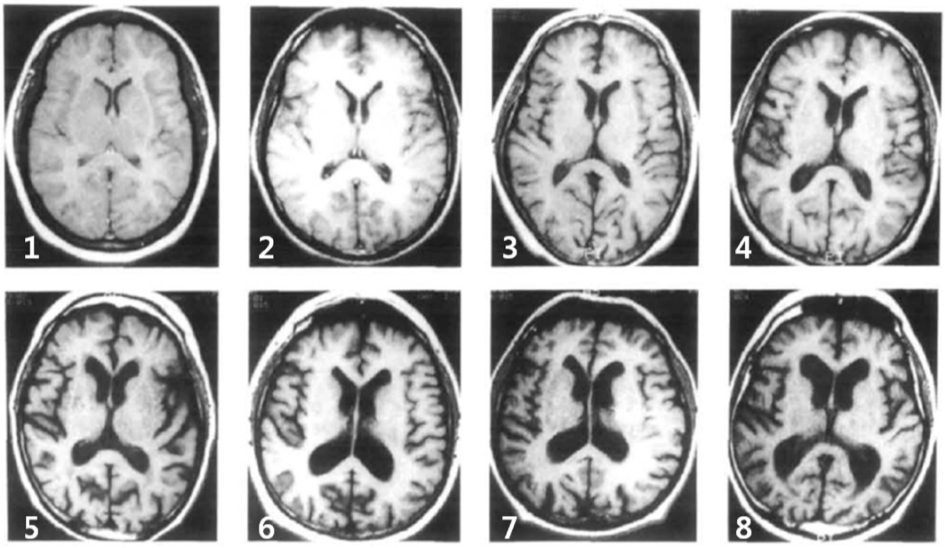

Figure 1: Degree of ventricular enlargement recommended by CHS (1~8).

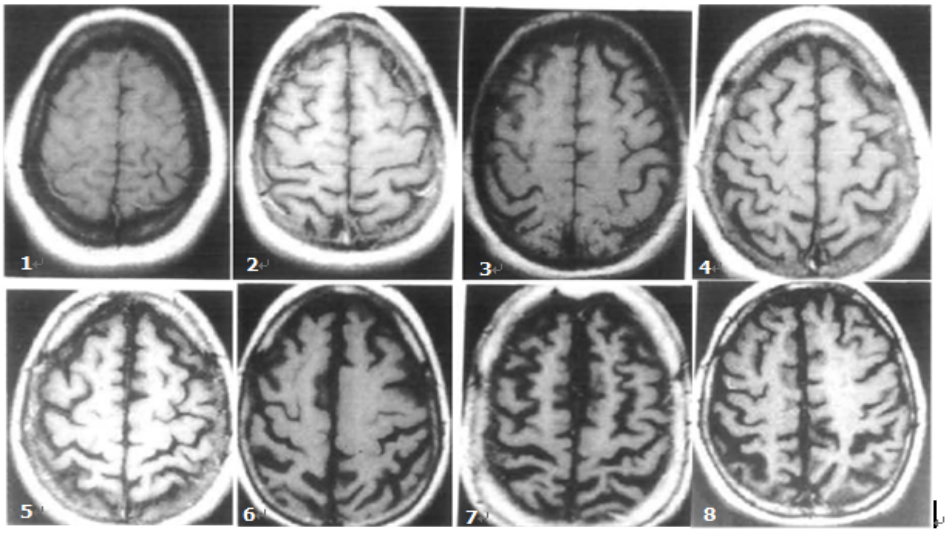

Figure 2: Degree of cortical atrophy recommended by CHS (1~8).

participants to evaluate cognitive status. These examinations were independently performed by a neuropsychologist who did not know clinical information of patients. All patients were undertaken the brain magnetic resonance imaging (MRI) (Achieva 3.0 TX Series of Philips). Brain MRI and neuropsychological tests were under routine test for new patients who were suggested PD. And these were conducted nearby.

We evaluated brain structural changes such as CA, VE, WMC and MTA with several visual scale systems. Ventricular size was assessed with the Cardiovascular Health Study (CHS) scales of 1 (presumable normal) to 8 (severe enlargement) using T1-weighted axial image (Figure **1**) [16]. CA was assessed with CHS scales with grade 1 to 8 (Figure **2**) [16]. WMC was estimated as the total volume of periventricular and subcortical white matter signal abnormality using T2-weighted image from barely detectable WMC (grade 1) to extensive, confluent changes (grade 8) (Figure **3**) [16]. A widely used standardized scale (Sheltens scale) was used to rate left and right MTA from T1-weighted coronal images. This scale rates atrophy as 0 (absent), 1 (minimal), 2 (mild), 3 (moderate) and 4 (severe) based on the width of the surrounding CSF spaces and the height of the hippocampal formation (Figure **4**) [17]. To get inter-rater and intra-rater agreement for visual rating, two neurologists who didn't know clinical information independently reviewed the brain MRI of the patients.

3. Statistical Analysis

SPSS-PC-software for Windows Version 20.0 was used for analysis. The frequency analysis and descriptive statistical analysis were conducted to

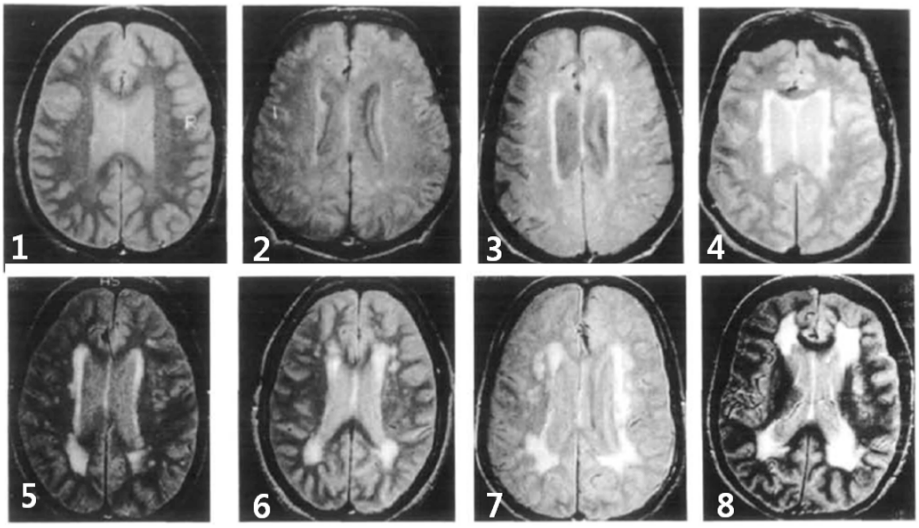

Figure 3: Severity of the cerebral white matter change shown by CHS scale (1~8).

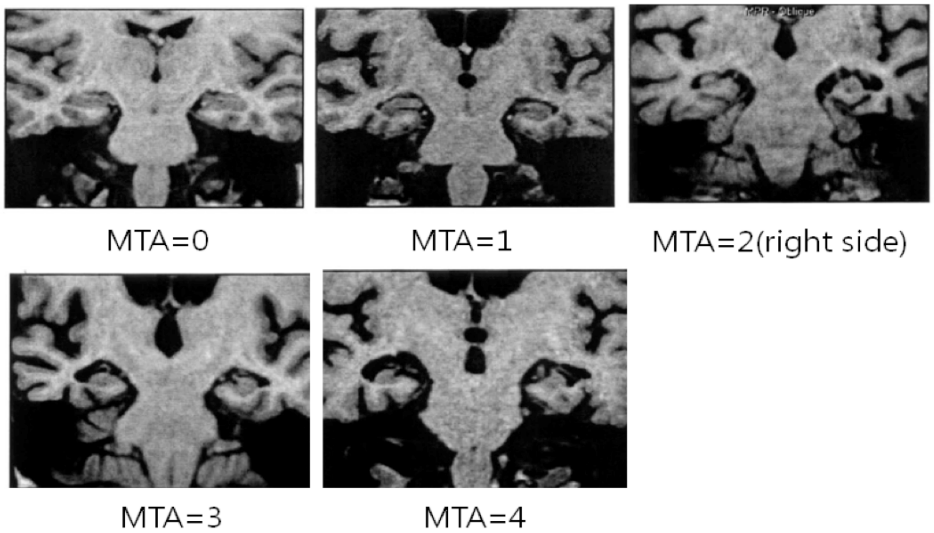

Figure 4: Severity of medial temporal lobe atrophy shown by Scheltens (0~4).

analyze mean and standard deviation of demographics, cognitive level, and the degree of motor symptoms of the patients. Correlation analysis was used to evaluate the relation between cognitive status and other clinical factors such as age, durations of education, H&Y stage, or structural changes of the brain. The analysis of covariate (ANCOVA) was conducted to analyze correlation brain structural change with cognitive decline or H&Y stage, after compensating age, sex and durations of education. Multiple linear regression was used to verify the most important clinical factor affecting on cognition. To identify inter-raters and intra-rater reliability for visual scoring of the brain MRI, the Cohen's kappa coefficient was calculated. The significance level was set at $p < 0.05$.

RESULTS

Mean age of the total subjects was 73.1 (52~87) years old and the ratio of men and women was 43:62. The participants had 6.2 years of mean durations of education (0~16 years). Average scores of the MMSE and 3MS were 22.3 and 67.8, respectively (Table **1**). There was no patient who was in H&Y stage 5. Lower cognitive function was associated with severe WMC, MTA, VE and CA of the brain in the total patients ($p<0.01$). As an expected, patients who showed higher level of cognitive function were younger age and had long durations of education (Table **2**).

Table 1: General Characteristics of the Total Participants

Variables	Total (n=105)
Demographics	
Age (years)	73.1 ± 7.9 (52~87)
Sex (M:F)	43 : 62
Duration of education (years)	6.2 ± 4.1 (0~16)
HTN (%)	36.2 % (n=38)
DM (%)	22.8 % (n=24)
Cognitive level	
MMSE	22.3 ± 4.8 (7~30)
3MS	67.8 ± 15.9 (17~94)
Characteristics of parkinsonism	
H-Y stage (n), 1 / 2 / 3 & 4	20 / 51 / 34
Disease duration (months)	26.3± 34.1 (1~180)

M; male; F: female; HTN: hypertension; DM: diabetes mellitus; MMSE: Korean version of the Mini-Mental State Examination; 3MS: Korean version of the modified Mini-Mental State examination; H-Y stage: Hoehn and Yahr stage.

Table 2: Variables Related with Cognitive Functions in Parkinson's Disease

Variables	MMSE	3MS
Clinical		
Age	-0.239 **	-0.264 **
Education	0.349 **	0.398 **
H-Y stage	-0.351 **	-0.316 **
Neuroimaging		
WMC	-0.286 **	-0.267 **
VE	-0.371 **	-0.321 **
MTA – R	-0.252 **	-0.297 **
MTA – L	-0.368 **	-0.368 **
CA	-0.324 **	-0.348 **

MMSE: Korean version of the Mini-Mental State Examination; 3MS: Korean version of the modified Mini-Mental State test; H-Y stage: Hoehn and Yahr stage; WMC: white matter change; VE: ventricular enlargement; MTA: medial temporal lobe atrophy; R: right; L: left; CA: cortical atrophy.
**p-value < 0.001.

The patients with more severe motor symptoms of PD had lower scores in the MMSE and 3MS, after adjustment of age, sex and durations of education. All evaluated structural changes of the brain except MTA became worse as clinical symptoms progressed (Table **3**).

Fifty seven patients of the total participants were classified as PD-CD subgroup (MMSE score < 24) and 48 patients were in PD-CP subgroup (MMSE ≥ 24). There was no statistical significant difference in age, durations of education and disease durations between two subgroups. Severity of WMC, VE and MTA was statistically worse in the PD-CD subgroup than the PD-CP subgroup (Table **4**).

The most relevant variables for cognitive impairment on the multiple linear regression analysis were the durations of education, degree of motor symptoms (H&Y stages), and MTA (Table **5**).

Cohen's kappa coefficients for inter-raters were 0.62~0.75 and those for intra-rater were 0.64~0.78, which were showed high level of agreement.

DISCUSSION

Results of Tam *et al*. study [11] showed absence of correlation temporal lobe atrophy with cognitive decline in PD patients using visual scale. However, we could find correlation cognitive function with brain structural lesion, especially medial temporal lobe atrophy using

Table 3: Comparison of Cognitive Function by the H-Y Stages

Variables	H-Y Stage 1 (n=20)	H-Y Stage 2 (n=51)	H-Y Stage 3 & 4 (n=34)	*p* Value
Cognition test				
MMSE	24.16 ± 0.9	22.58 ± 0.6	20.70 ± 0.7	0.000**
3MS	74.57 ± 3.2	67.38 ± 1.9	64.43 ± 2.4	0.000**
Neuroimaging				
WMC	2.79 ± 0.3	2.98 ± 0.2	3.41 ± 0.3	0.010*
VE	3.03 ± 0.3	4.10 ± 0.2	4.29 ± 0.2	0.003*
MTA	0.94 ± 0.5	2.66 ± 0.3	2.22 ± 0.4	0.002*
MTA – R	0.45 ± 0.3	1.25 ± 0.2	1.06 ± 0.2	0.001*
MTA - L	0.49 ± 0.2	1.41 ± 0.2	1.15 ± 0.2	0.006*
CA	3.39 ± 0.3	2.96 ± 0.2	3.24 ± 0.2	0.005*

Age, sex, and duration of education are adjusted by ANCOVA.
H-Y stage: Hoehn and Yahr stage; MMSE: Korean version of the Mini-Mental State Examination; 3MS: Korean version of the modified Mini-Mental State test; WMC: white matter change; VE: ventricular enlargement; MTA: medial temporal lobe atrophy; R: right; L: left; CA: cortical atrophy.
***p*-value < 0.001; * *p*-value < 0.05.

Table 4: Comparison of the Structural Change of the Brain between Cognitively Declined (PD-CD) *vs*. Cognitively Preserved (PD-CP) Subgroups

Variables	PD-CD (n=57)	PD-CP (n=48)	*p* Value
Clinical			
Age (years)	74.5± 6.0	71.5 ± 9.6	0.359
Sex (M:F)	19 : 38	24 : 24	0.111
Duration of education (years)	5.5± 3.9	6.9 ± 4.3	0.061
Disease duration (months)	28.5± 33.4	23.7± 35.1	0.476
Neuroimaging			
WMC	± 1.8	2.63 ± 1.6	0.013*
VE	3.51 ±1.6	3.31 ± 1.5	0.000**
MTA – R	2.88 ± 2.4	1.38 ± 1.6	0.000**
MTA – L	1.35 ± 1.3	0.67 ± 0.9	0.003*
MTA	1.53 ± 1.2	0.71 ± 0.8	0.000*
CA	3.21 ± 1.5	3.04 ± 1.4	0.558

WMC: white matter change; VE: ventricular enlargement; MTA: medial temporal lobe atrophy; R: right; L: left; CA: cortical atrophy.
***p*-value < 0.001; **p*-value < 0.05.

visual rating scales. It made reinforce the suggestion that pathology of cognitive declined in PD include coexistent Lewy body degeneration and Alzheimer-type change by neuroanatomical correlations.

Up to 80% of PD patients have cognitive decline or dementia [18]. Although the subjects or methods of many previous studies were heterogeneous, older age of onset, more severe motor symptoms, gait disturbance-dominant type or depressive mood were known risk factors of PDD. This study also showed that the patients with cognitive impairment had a tendency to be older, less educated, and more advanced stage of PD.

Previous studies presented that increasing Parkinson's disease severity were independent contributors to cognitive decline [19]. In our study, advanced stage of PD patients (higher H&Y stages) showed more severe structural changes of the brain

Table 5: Variables Related with Cognitive Dysfunction by Multiple Linear Regression

Variables	K-MMSE		3MS	
	R^2	*p* Value	R^2	*p* Value
Clinical				
Age	0.057	0.871	0.070	0.864
Sex	0.084	0.769	0.135	0.756
Education	0.122	0.001*	0.159	0.000**
H-Y stage	0.123	0.003*	0.100	0.012**
Neuroimaging				
WMC	0.082	0.780	0.071	0.775
VE	0.137	0.487	0.103	0.479
MTA	0.105	0.087	0.121	0.000**
MTA-R	0.063	0.303	0.088	0.080
MTA-L	0.136	0.001*	0.135	0.087

MMSE: Korean version of the Mini-Mental State Examination; 3MS: Korean version of the modified Mini-Mental State test; H-Y stage: Hoehn and Yahr stage; WMC: white matter change; VE: ventricular enlargement; MTA: medial temporal lobe atrophy; L: left; R: right.
**p-value < 0.001; *p-value < 0.05.

and worse cognitive function, after adjustment of age, gender and duration of education.

In previous studies, PDD patients had severe changes of MTA, CA and WMC [11, 20-23]. PD patients with mild cognitive impairment or without cognitive dysfunction presented more severe atrophy of medial temporal lobe than normal control group [20]. Two subgroups which were PD-CP and PD-CD presented that the degree of WMC, VE and MTA in the PD-CD was more severe than those of PD-CP. Among them, MTA is the most relevant associated factor to cognitive decline. These results suggest that medial temporal lobe atrophy is an important cause of cognitive decline in PD.

Lewy body deposition which already known as pathology of Parkinson's disease is spread from olfactory bulb and lower brainstem to limbic system and cortex following disease progression [24]. So, this is related with advanced stage of PD have lower cognitive function.

Model of dynamic biomarkers of pathological cascade for Alzheimer's disease, starting with evidence of beta-amyloidosis, is followed by neuronal dysfunction and neurodegeneration [25]. Alzheimer disease pattern of atrophy, like MTA, is correlated with global cognitive performance and associated with progression of cognitive decline in PD [19]. Some recent studies suggest that amyloid deposition in the brain can be an important contributor for cognitive dysfunction in PD [26, 27]. In our study, MTA and H &Y stage are the most relevant and independent compositions for cognitive decline in PD. Although we did not evaluate pathological changes of the brain in this study, it is possible to conclude that the brain atrophy, especially MTA, in the PD patients may result in cognitive dysfunction irrespective of amyloid deposition.

Our study has advantages in that we included more patients than previous studies, increased reliability of visual rating scales by conducting statistical analysis of inter-rater and intra-rater. Besides, since we excluded patients who have long time intervals between brain MRI and MMSE and 3MS examination, we were able to decrease time error of disease severity. Limitation of this study is that mostly consisted of mild and moderate Parkinson's disease patients and conducted retrospectively., Therefore, we should conduct further prospective study with severe patients and a control group to investigate the relation between brain structural change and cognitive function.

In conclusion, older age, less education and advanced stage of PD as well as severe structural changes of the brain, including WMC, VE, and MTA are responsible for cognitive impairment or dementia in PD patients. And the structural change of the brain including MTA can be a biomarker of cognitive decline in PD. Therefore, clinicians need thorough regular evaluation of the neuropsychological assessment to define cognitive function as well as neuroimaging for early therapeutic intervention.

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