Cerebral microbleeds in patients with Parkinson's disease according to cognitive status

Jee Hyun Ham

The Graduate School

Yonsei University

Department of Medicine

Cerebral microbleeds in patients with Parkinson's disease according to cognitive status

Directed by Professor Ji-Yong Lee

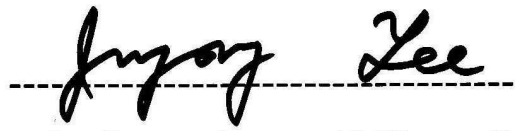
The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

Jee Hyun Ham

June 2014

This certifies that the Master's Thesis of

Jee Hyun Ham is approved.



Thesis Supervisor : Ji-Yong Lee

Thesis Committee Member #1: Sung Soo Lee

Thesis Committee Member #2: Seo Hyun Kim

The Graduate School

Yonsei University

June 2014

ACKNOWLEDGEMENTS

I would like to express heartfelt thanks to professor Sung Su Lee, professor Ji-Yong Lee and professor Seo Hyun Kim for careful concern and magnanimous advice.

I would like to appreciate to my supervisor Professor Phil Hyu Lee for his valuable and constructive suggestions during the planning and development of this research work. I have learned a lot under his tutelage.

I love and give special thanks to my parents for their invaluable support and love. I thank my parents in law who help me both physically and spiritually, too. Finally I'm deeply grateful to the most precious Jae Hwang and Si Hyun in my life.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Cerebral microbleeds in patients with Parkinson's disease according to cognitive status

Jee Hyun Ham

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Ji-Yong Lee)

Cerebral microbleeds (CMBs) are known to be associated with cognitive impairments in the elderly and in patients with various diseases, however, the nature of this association has not yet been evaluated in Parkinson's disease (PD). In the present study, we analyzed the incidence of CMBs in PD according to cognitive status, and the impact of CMBs on cognitive performance was also evaluated. The CMBs in PD with dementia (n=36), mild cognitive impairment (MCI, n=46), or cognitively normal (n=41) were analyzed using a conventional T2* weighted gradient recalled echo images. Additionally, the relationship between the presence of CMBs and cognitive performance on individual tests of cognitive subdomains was analyzed using a detailed neuropsychological test. CMBs occurred more frequently in PD patients with dementia (36.1 %) compared to those with MCI (15.2%), those who are cognitively normal (14.6%), and normal controls

(12.2%, p=0.025). However, the significant association of CMBs with PD dementia disappeared after adjusting white matter hyperintensities (WMHs) as a covariate. The frequencies of deep, lobar, and infratentorial CMBs did not differ among the four groups. After adjusting for age, sex, years of education, and WMHs, PD patients with CMBs had poorer performance in attention domain compared with those without CMBs (34.9 vs 42.6, p=0.018). The present data demonstrate that even though CMBs was inseparably associated with the presence of WMHs, CMBs occur more commonly in PD patients with dementia than in those without dementia. Additionally, the burden of CMBs may contribute to further cognitive impairment in PD.

Key words : cerebral microbleeds, Parkinson's disease, cognitive performance

Cerebral microbleeds in patients with Parkinson's disease according to cognitive status

Jee Hyun Ham

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Ji-Yong Lee)

I. INTRODUCTION

Cognitive impairments are common in Parkinson's disease (PD), being one of most disabling non-motor aspects of PD. Patients with PD have three-to-six times higher risk of developing dementia relative to controls,[1] and an mean prevalence of dementia in PD (PDD) is 40%.[2] Moreover, recent epidemiological studies have found that one fifth of PD patients and about 19% of patients with untreated early PD exhibit mild cognitive impairments (MCI).[3]

A number of possible candidates for the neurochemical and pathological mechanisms underlying PD-related cognitive dysfunction have been suggested. Of those, α-synuclein, a major component of Lewy bodies, is a key pathological contributor to development of dementia in PD.[4] In addition, Alzheimer's disease (AD) pathologies of β-amyloid plaques and neurofibrillary tangles, which coexist in PD pathology, may influence the onset and progression rate of dementia in

patients with PD.[5] Furthermore, recent studies have demonstrated that vascular pathologies, such as cerebral white matter hyperintensities (WMHs) and multiple lacunes are more severe in patients with PDD compared to those without dementia.[6] Cerebral microbleeds (CMBs) are small, rounded, homogenous, hypointense lesions on T2*-weighted gradient-recalled echo (T2*-weighted GRE),[7] which are correlated histologically to hemosiderin deposit from blood-breakdown products that leaked from small vessels.[8] CMBs are related primarily to pathological processes that affect small arteries, arterioles, and capillaries of the brain, which include hypertensive vasculopathy and cerebral amyloid angiopathy (CAA).[9] Moreover, the presence of CMBs is known to impact cognitive performance in normal age subjects[10] and in those with various diseases,[11-13] however, their influence on cognition in patients with PD has not been evaluated. The present study tested the hypothesis that CMBs would be observed more frequently in patients with PDD, where the burden of vascular pathology or PD-related toxic protein aggregates is more severe, than in those without dementia. Thus, the present study analyzed the incidence of CMBs in patients with PD according to cognitive status, and assessed whether the presence of CMBs influences cognitive performance in these patients.

II. MATERIALS AND METHODS

1. Subjects

For this study, we retrospectively enrolled 123 patients with PD from a university hospital between January 2008 and January 2013. PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank,[14] and these patients were classified into PDD (n=36), PD-MCI (n=46), and

PD-cognitively normal (PD-CN, n=41) according to cognitive status. For subjects with a diagnosis of PD-MCI or PDD, the Seoul Neuropsychological Screening Battery (SNSB) was used to determine impairments in specific cognitive subsets.[15] The SNSB covers attention, language, visuoconstructive function, verbal and visual memory, and frontal/executive function. For these, the quantifiable tests comprised the a digit span task (forward and backward), the Korean version of the Boston Naming Test (K-BNT),[16] the Rey Complex Figure Test (RCFT; copying, immediate and 20 min delayed recall, and recognition), the Seoul Verbal Learning Test (SVLT; three free recall trials of 12 words, a 20 min delayed recall trial for the 12 items and a recognition test), phonemic and semantic Controlled Oral Word Association Test (COWAT), a go-no-go test and contrasting programming, and the Stroop Test (word and color reading of 112 items over a 2 min period). Age, sex and education specific norms for each test based on 447 normal subjects are available. The scores on the sequantifiable cognitive tests were classified as abnormal if they were below the 16th percentile of the norms for age, sex and education matched normal subjects.

PD-CN was defined as no objective cognitive dysfunction. To diagnose PD-MCI, two neuropsychological tests were designated to represent each of the four domains except the language domain. Attention was tested with a digit span task and the Stroop color-word test, executive function was tested using the COWAT and a clock drawing test, memory was tested using the SVLT and the RCFT, visuospatial function was tested using the RCFT copy and a pentagon drawing test, and the language domain was tested using only the K-BNT. Following the Movement Disorder Society Task Force guidelines,[17] the diagnosis of MCI in patients with PD was made if at least two tests for each of the four

domains, except the language domain (level 2) or for all five domain (level 1) were abnormal. All PD-MCI patients expressed a subjective cognitive complaint, scores of the Korean version of the Mini Mental State Examination (K-MMSE) above the 16th percentile for age- and education-appropriate norms and also showed no evidence of abnormal activities of daily living. PDD was diagnosed according to the clinical diagnostic criteria for probable PDD.[18] Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III (UPDRS-III).[19] The basic demographic data for gender, age, and history of hypertension, diabetes mellitus, coronary artery obstructive disease, or cerebrovascular accidents were also analyzed. A history of hypertension was defined as prior physician-diagnosed hypertension with or without the use of antihypertensive agents, and a history of diabetes was defined based on self-report or the use of hypoglycemic agents.

Exclusion criteria included evidence of focal brain lesions on magnetic resonance imaging (MRI) or the presence of other neurodegenerative diseases that might account for dementia. Possible medical comorbidities were also excluded by laboratory tests, including thyroid function tests, vitamin B12 and folic acid levels, and the VDRL test. Patients with a pharmacological history of drugs that induce parkinsonism (*e.g.*, antipsychotics, gastrointestinal kinetics, antiepileptic drugs, or L-type calcium channel blockers) were excluded. A [18F] FP-CIT PET scan was performed on 94 of the study subjects, and all showed decreased dopamine transporter uptake in the posterior putamen. Healthy age- and gender-matched elderly volunteers were used as controls for the CMBs analysis. They were recruited by advertisements about the project or were healthy relatives of patients with movement disorders or dementia (n = 49, age = 70.4 yr). The controls did

not have active neurological disorders, or cognitive complaints, and exhibited normal performance on neuropsychological tests, with a minimum score of 27 on the K-MMSE. Informed consent was obtained from all patients and control subjects. This study was approved by the Institutional Review Board of Yonsei University Severance Hospital.

2. Brain MRI

All scans of healthy controls and PD patients were acquired using a 3.0-T system (Intera or Achieva, Philips Medical System, Best, The Netherlands). A conventional 2D T2*-weighted GRE in the axial plane was obtained with the following parameters: 500-680/15 (TR/TE), a flip angle of 18°, and section thickness of 5 mm. CMBs were defined as a small, rounded, homogenous, hypo-intense lesions on T2*-weighted GRE sequences for which more than half was surrounded by brain parenchyma (Figure 1). The lesions were distinct from other factors that can mimic CMBs, including vessel flow voids, calcification, or iron deposits. Flow voids of pial blood vessels in cortical sulci can be distinguished by identifying their location and linear structure. Additionally, areas of symmetric hypointensity of the globus pallidus that were likely to represent calcification or iron deposits were excluded.[7] Based on anatomical location, CMBs were classified as deep (lesions in caudate, thalamus, putamen, globus pallidus, corpus callosum, internal capsule, or external capsule), lobar (lesions in frontal, parietal, temporal, or occipital lobes or the periventricular area), or infratentorial (lesions in brainstem or cerebellum).[20] CMBs in each anatomical location were checked by two neurologists (H.J.H. and Y.H.) who were blind to the clinical data. The reliability of the data was assessed using Cohen's kappa. The intra- and

inter-rater reliabilities, expressed as kappa coefficients, were 0.88 and 0.80, respectively. The Age-Related White Matter Change rating scale proposed by Wahlund et al.[21] was used to grade WHMs. Briefly, a four-point grading scale (0: normal; 1: focal lesion; 2: beginning confluence; 3: diffuse involvement) is applied to five regions (frontal, parieto-occipital, temporal, infratentorial, and basal ganglia); the total score ranges from 0 to 30. WMH scores were rated blindly (H.J.H. and S.M.K.), and the intra- and inter-scorer reliability (expressed as correlation coefficients) were 0.93 and 0.86, respectively.

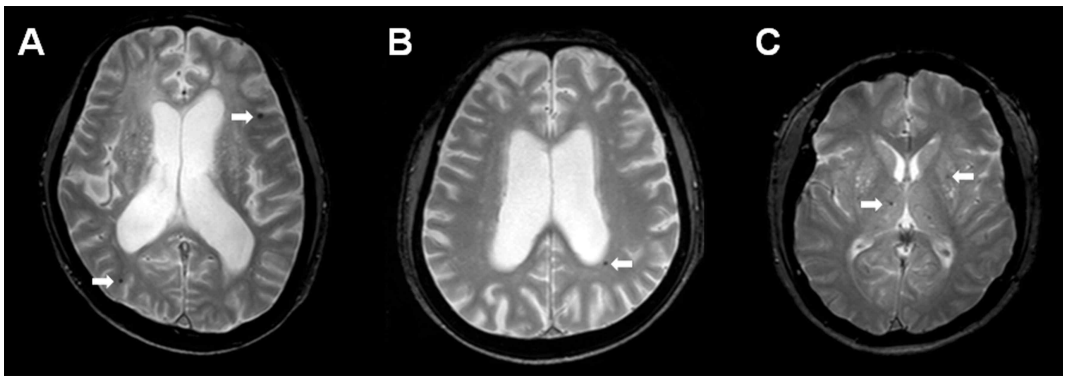


Figure 1. Axial MRI obtained with conventional 2D T2*-weighted GRE sequences. MRI from a patient with Parkinson's disease (PD)-dementia exhibits multiple cerebral microbleeds (CMBs) in the right occipital lobe and left frontal lobe (A). MRI from a patient with PD-mild cognitive impairment shows a right periventricular CMB (B), and MRI from a patient with PD-cognitively normal shows bilateral thalamic and basal ganglia CMBs (C).

3. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 18.0 (SPSS, Inc.; Chicago, IL, USA). The baseline demographic characteristics of the four groups were compared using an analysis of variance test or the Chi-Square test for continuous and categorical variables, respectively. The Chi-square test was used to compare the number of patients with CMBs among the four groups with a p value < 0.05 considered to be significant. *Post hoc* analyses included a Bonferroni test performed to compare the means of the four groups. Additionally, a multiple logistic regression analysis adjusting for age, sex, hypertension, and scales for white matter hyperintensities was performed to assess the contribution of various factors towards the occurrence of CMBs with a multiple testing correction to adjust the individual p-value for 6 groups. A composite score, dividing the sum by number of tests in each cognitive domain, was used to form reliable measures and an analysis of covariance was used to compare the results of the neuropsychological tests and was adjusted for age, sex, years of education, and scale of WMHs.

III. RESULTS

1. Demographic charateristics

The demographic characteristics of the subjects are provided in Table 1. No significant differences were found among the four groups for age, gender, education level, vascular risk factors, or vascular events. Scores of WMHs were significantly higher for patients with PDD than for PD-MCI (0.025) and PD-CN patients (p= 0.036) and controls (p= 0.019), but there were no significant

differences between PD-MCI and PD-CN patients or PD-MCI patients and controls.

Table 1. Demographic characteristics between Parkinson's disease with dementia (PDD), PD with mild cognitive impairment (PD-MCI), PD with cognitively normal (PD-CN), and normal controls

	PDD	PD-MCI	PD-CN	Control	*p-value*
N	36	46	41	49	
Age (years)	69.8 (5.9)	70.3 (8.1)	69.0 (6.1)	70.4 (6.7)	0.688
Gender (men)	20 (55.6)	25 (54.3)	15 (36.6)	19 (38.8)	0.164
Hypertension	16 (44.4)	12 (26.1)	12 (29.3)	21 (42.9)	0.180
DM	8 (22.2)	9 (19.6)	6 (14.6)	8 (16.3)	0.821
Ischemic stroke	7 (19.4)	5 (10.9)	4 (9.8)	4 (8.2)	0.411
CAOD	4 (11.1)	9 (19.6)	3 (7.3)	7 (14.3)	0.389
Cholesterol (mg/dl)	170.9 (37.8)	173.9 (34.5)	188.0 (35.8)	178.2 (37.7)	0.227
WMHs	2.8 (3.4)	1.39 (1.9)	1.41 (1.8)	1.37 (1.65)	0.009
UPDRSIII	34.2 (13.6)	29.4 (10.9)	22.9 (9.4)		< 0.001
K-MMSE	18.7 (3.5)	25.7 (3.5)	28.1 (1.9)	27.6 (2.3)	< 0.001
Education (years)	7.6 (4.8)	10.6 (19.3)	9.6 (6.0)	7.5 (6.0)	0.474

Values are expressed as number of subjects (%) or mean ± SD.
DM: Diabetes Mellitus, CAOD: Coronary Artery Obstructive Disease, WMHs: White Matter Hyperintensities, UPDRSIII: Unified Parkinson's Disease Rating Scale part III, K-MMSE: Korean Mini-Mental State Examination

2. CMBs in PD according to cognitive status

Analysis of CMBs among the four groups is shown in Table 2. CMBs were detected more frequently in patients with PDD (36.1%) compared to PD-MCI (15.2%) and PD-CN (14.6%) patients and normal controls (12.2%, p=0.025). *Post*

hoc analyses revealed that the frequency of CMBs in PDD patients was greater than that in PD-MCI patients (p=0.029), PD-CN patients (p=0.029), and normal controls (p=0.009). The frequency of CMBs in PD-MCI patients did not significantly differ relative to PD-CN patients and control subjects. Analysis of CMBs according to location revealed that the frequencies of deep CMBs, lobar CMBs, and infratentorial CMBs did not differ among the four groups. Moreover, when using WMHs as a covariate, multiple logistic regression analyses did not find a significant association of CMBs in PDD patients compared to patients with non-demented PD (Table 3).

3. The effect of CMBs on cognition in patient with PD

Finally, whether the presence of CMBs contributes to cognitive dysfunction in patients with PD was evaluated. After adjusting for age, sex, years of education, and scale of WMHs, PD patients with CMBs had lower scores in word Stroop tasks (81.8 versus 100.1), visual delayed memory (7.0 versus 10.6), and phonemic fluency (10.3 versus 16.3) than in those without CMBs. No differences in the other cognitive subdomains were observed between the groups. However, all detailed tasks did not reach a statistical significance after correction for multiple comparisons (table 4). When the composite scores were compared, PD patients with CMBs had poorer performance in only attention domain compared to those without CMBs (34.9 vs 42.6, p=0.018). The composite scores in executive function domain tended to be lower in PD patients with CMBs than in those without CMBs (12.2 vs 14.1). The composite scores in other functional domains did not differ significantly between groups.

Table 2. Cerebral microbleeds (CMBs) in Parkinson's disease with dementia (PDD), PD with mild cognitive impairment (PD-MCI), PD with cognitively normal (PD-CN), and normal controls

N (%)	PDD (n=36)	PD-MCI (n=46)	PD-CN (n=41)	Control (n=49)	*p-value*†	PDD vs PD MCI‡	PDD vs PD CN‡	PDD vs Control‡
Microbleeds	13 (36.1)	7 (15.2)	6 (17.1)	6 (12.2)	0.025	0.029	0.029	0.009
Deep	4 (11.1)	3 (6.5)	2 (4.9)	0 (0.0)	0.146	0.460	0.309	0.017
Lobar	4 (11.1)	4 (8.7)	2 (4.9)	5 (10.2)	0.764	0.714	0.309	0.893
Infratentorial	2 (5.6)	1 (2.2)	1 (2.4)	0 (0)	0.419	0.418	0.481	0.095
Mixed A	1 (2.8)	0 (0.0)	1 (2.4)	1 (2.0)	0.757	0.255	0.481	0.386
Mixed B	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		0.284	0.255	0.283
Mixed C	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0.284	0.255	0.283	0.241
Mixed D	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0.284	0.255	0.283	0.241
No. of CMBs*	3.3 (7.2)	1.0 (0.0)	1.8 (2.0)	1.7 (1.2)	0.764	>0.999	>0.999	>0.999

Values are expressed as number of subjects (%) or mean (standard deviation)*.

Mixed A: patients having both deep and lobar CMBs. Mixed B: patients having both deep and infratentorial CMBs.

Mixed C: patients having both lobar and infratentorial CMBs. Mixed D: patients having both deep, lobar, and infratentorial CMBs.

†p-value from Chi-square test or Fisher's exact test. ‡Bonferroni corrected p-values of the post-hoc pairwise comparison tests.

Table 3. Multivariate logistic analysis of determinants for cerebral microbleeds

	Odd's ratio (95% CI)	*p-value**
		0.201
PDD vs PD-MCI	2.221 (0.683-7.219)	> 0.999
PDD vs PD-CN	2.381 (0.711-7.968)	> 0.999
PDD vs control	3.136 (0.949-10.360)	0.366
PD-MCI vs PD-CN	0.936 (0.275-3.183)	> 0.999
PD-MCI vs control	1.267 (0.375-4.277)	> 0.999
PD-CN vs control	1.357 (0.387-4.763)	> 0.999

On multivariate analysis, data are adjusted for age, sex, hypertension, and scales for white matter hyperintensities.

*A multiple testing correction to adjust the individual p-value for 6 groups.

PDD: Parkinson's disease with dementia, PD-MCI: PD with mild cognitive impairment, PD-CN: PD with cognitively normal.

Table 4. Neuropsychological data in Parkinson's disease according to the presence of cerebral microbleeds (CMBs)

	CMB (+) (n=26)	CMB (-) (n=96)	*p-value*
Basic characteristics			
Age (years)	71.4 ± 6.7	69.2 ± 6.8	0.150
Sex (no of male)	14 (51.9)	46 (47.9)	0.718
Education year (years)	12.4 ± 24.9	8.6 ± 5.4	0.162
MMSE	23.5 ± 4.8	24.8 ± 4.9	0.239
WMHs	3.1 ± 3.7	1.5 ± 1.8	0.001
Attention	34.9 ± 2.7	42.6 ± 1.4	0.018*
Digit span (forward)	5.9 ± 1.3	5.6 ± 1.5	0.183
Digit span (backward)	2.9 ± 1.4	3.7 ± 1.9	0.061
Word Stroop test	81.8 ± 37.6	100.1 ± 25.6	0.019
Color Stroop test	46.7 ± 33.2	59.6 ± 34.4	0.162
Language and related function	23.7 ± 1.2	25.6 ± 0.6	0.180*
K-BNT	33.5 ± 12.3	37.2 ± 11.8	0.144
Repetition	14.0 ± 1.9	14.1 ± 1.5	0.967
Visuospatial function	13.4 ± 1.6*	16.6 ± 0.8*	0.092*
RCFT	21.4 ± 12.7	28.4 ± 14.9	0.110
Pentagon drawing test	4.9 ± 1.3	5.1 ± 1.3	0.983
Verbal memory function (SVLT)	10.8 ± 0.8	10.7 ± 0.4	0.881*
Immediate recall	14.4 ± 6.4	15.3 ± 6.2	0.879
Delayed recall	3.0 ± 3.2	4.1 ± 3.0	0.374
Recognition	14.1 ± 5.4	13.0 ± 5.2	0.312
Visual memory function (RCFT)	9.8 ± 4.7	11.7 ± 4.7	0.169*
Immediate recall	7.9 ± 6.2	11.3 ± 6.9	0.069
Delayed recall	7.0 ± 6.3	10.6 ± 6.7	0.039
Recognition	14.7 ± 5.4	13.1 ± 5.1	0.186
Frontal executive function	12.2 ± 1.0	14.1 ± 0.5	0.097*
Contrasting program	14.6 ± 7.8	17.4 ± 5.3	0.131
Go-no-go test	12.2 ± 8.5	15.6 ± 6.1	0.101
Phonemic generative naming	10.3 ± 8.6	16.3 ± 11.2	0.018
COWAT (Animal)	9.9 ± 4.8	11.7 ± 4.6	0.284
COWAT (Supermarket)	11.1 ± 7.0	12.8 ± 6.6	0.460
Clock drawing test	8.5 ± 1.5	8.9 ± 1.6	0.345

Values are expressed as mean ± SD.
Data are adjusted for age, sex, years of education and white matter hyperintensity scale.
*Group comparison with composite scores for cognitive domains.
CMBs: cerebral microbleeds, K-BNT: Korean version of Boston Naming Test, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, COWAT: Controlled Oral Word Association Test.

IV. DISCUSSION

The present study demonstrates for the first time that CMBs are observed more frequently in patients with PDD compared to PD-MCI and PD-CN patients and control subjects, even though the presence of CMBs was inseparably associated with the presence of WMHs. Additionally, the presence of CMBs in patients with PD may have a negative impact on cognitive performance of attention-associated domain. These data suggest that the burden of CMBs might serve as one of contributors to the development of cognitive dysfunction in patients with PD.

CMBs are associated with hypertensive vasculopathy and cerebral amyloid angiopathy (CAA) and the pattern of its distribution usually differs according to the pathological process involved. Hypertensive vasculopathy typically affects small perforating arterioles in deep gray matter, thus resulting in CMBs in the basal ganglia, thalamus, brainstem, and cerebellum.[22] In contrast, CAA generally involves leptomeningeal and cortical arterial vessels,[23] thus leading to a lobar distribution of CMBs.[24] In the current study, CMBs were found more frequently in patients with PDD compared to non-demented PD patients and controls, and were distributed evenly in deep, lobar, and infratentorial structures without a specific predilection. This suggests that vascular pathology associated with

traditional vascular risk factors as well as CAA may contribute equally to development of CMBs in patients with PDD relative to patients with non-demented PD.

Even though it is difficult to explain why CMBs are more frequently observed in patients with PDD, it may be speculated that multiple interacting factors are involved. First, supine hypertension accompanied by autonomic failure in PD may lead to hypertensive vasculopathy-related CMBs. Importantly, recent evidence has demonstrated that the degree to which cognitive deficits exist is closely coupled to the severity of autonomic dysfunction,[25-27] which supports an association between CMBs and supine hypertension. Second, WMHs are suggested to be closely associated with the presence of CMBs because these lesions share common underlying pathomechanisms of microangiopathy.[28-30] The present study also showed that the presence of CMBs was also inseparably associated with the occurrence of WMHs based on the fact that the significant association of CMBs with PDD disappeared after adjusting WMH as a covariate. Although the pathophysiology of underlying WMHs is not completely understood, these lesions are highly associated with age[31] and the presence of traditional vascular risk factors.[32,33] In present study, age and traditional vascular risk factors relevant to atherosclerotic vasculopathy did not significantly differ among the PD groups, indicating that other nonvascular factors may contribute to WMHs. Of these factors, hypotensive episode-induced cerebral hypoperfusion secondary to autonomic dysregulation could play an important role in the development of WMHs.[34] Additionally, we recently reported that patients with PD who chronically receive levodopa exhibit decreases in their level of endothelial progenitor cells (EPCs),[35] a marker of endothelial function and an indicator of increased vascular risk.[36]

Because decreased levels of EPCs are associated with the burden of WMHs,[37] it is possible that an abnormal endothelial repair process in PD patients with chronic levodopa treatment may partially contribute to the development of WMH. Finally, recent pathological and imaging studies provide evidence that alteration of the blood-brain barrier (BBB) leading to extravasation of blood components, a form of CAA, can contribute to the development of WMHs.[38,39] In patients with PD, the BBB is known to be altered, and BBB impairment is more severe in the advanced stage of PD.[40,41] Thus, severe impairment of the BBB integrity in patients with PDD may impact the severity of WMHs. Finally, ethnic difference may influence the WMH-related vasculopathy, because Asian ethnicity is known to have a higher prevalence of WMHs than the Caucasian population.[42,43]

Although several studies have suggested that CMBs are clinically silent or unrelated to general cognitive performance,[44,45] more recent studies have suggested a close relationship between cognition and CMBs in different disease entities, for example, in patients with stroke, several studies have found a relationship between executive dysfunction and CMBs independently of the white matter changes evident on MRI,[46] and a similar association was also identified in patients with symptomatic small vessel disease.[47] Additionally, in patients with Alzheimer's disease, multiple CMBs had more severe cognitive impairment that could not be explained by the degree of atrophy or WMHs.[48] Likewise, the present study demonstrated that the presence of CMBs has a negative impact on cognitive performance, especially on attention-related cognitive domains, independently of the severity of the WMHs. The pathomechanisms underpinning the influence of CMBs on attention-related cognitive performance remain unknown; however, the present results suggest that that even though the presence of CMBs may be closely linked

with WMHs, CMBs may have an impact on cognition in a way different from WMHs. As suggested by Yakushiji and colleagues,[10] one speculation is that CMBs may directly disrupt cortical-subcortical connections via the effects of lesions, particularly cholinergic projections from the basal forebrain because the cholinergic system has an important role in sustained attention through interaction with frontal lobe and thalamocortical processing.[49] Alternatively, it is possible that the CMBs may indirectly influence cognitive performance through the underlying microangiopathic process. Accordingly, our findings suggest that, along with the pathological burden of α-synuclein, CMBs may contribute to the additive burden of cognitive dysfunction in patients with PD.

Several limitations of the present study should be addressed. Because this was a retrospective study from one hospital, selection biases may have influenced the determination of the study population in terms of the incidence of CMBs. Second, this study used conventional 2D T2*-weighted GRE, which is less sensitive than 3D T2*-weighted GRE for detecting CMBs, and this may have underestimated the number of CMBs. Additionally, evidence is emerging for a different distribution of CMBs depending on ethnicity; most CMBs in Caucasians are located in lobar areas, whereas CMBs in Asian ethnicity exhibits deep locations.[50,51] This ethnic factor should be carefully considered in interpretation of the present results. Third, although dopamine transporter imaging was used to determine underlying PD pathology in about 76% of the study subjects, this study is not autopsy-proven data and thus, we could not completely exclude the influence of AD-like pathology. Forth, although the scoring method used for WMHs has been widely used and was performed by blinded investigators, this visual rating method is less objective than a volumetric analysis. Finally, this was a cross-sectional study, and

thus its clinical significance of CMBs as a predictor of ongoing cognitive decline should be interpreted cautiously.

V. CONCLUSION

In summary, the present study found that CMBs occur more frequently in patients with PDD than in those with non-demented PD and may contribute to an exacerbation of further cognitive impairments in patients with PD. A longitudinal study is necessary to clarify whether the presence of CMBs constitutes as an additive burden of ongoing cognitive dysfunction.

REFERENCES

1. Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P (2001) Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology 56:730-736
2. Cummings JL (1988) Intellectual impairment in Parkinson's disease: clinical, pathologic, and biochemical correlates. J Geriatr Psychiatry Neurol 1:24-36
3. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G (2009) Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology 72:1121-1126. doi: 10.1212/01.wnl.0000338632.00552.cb
4. Emre M (2003) Dementia associated with Parkinson's disease. Lancet Neurol 2:229-237
5. Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton JL, Collins C, Lashley T, Kallis C, Williams DR, de Silva R, Lees AJ, Revesz T (2011) Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain 134:1493-1505. doi: 10.1093/brain/awr031
6. Shin J, Choi S, Lee JE, Lee HS, Sohn YH, Lee PH (2012) Subcortical white matter hyperintensities within the cholinergic pathways of Parkinson's disease patients according to cognitive status. J Neurol Neurosurg Psychiatry 83:315-321. doi: 10.1136/jnnp-2011-300872
7. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM (2009)

Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 8:165-174. doi: 10.1016/s1474-4422(09)70013-4

8. Fisher M, French S, Ji P, Kim RC (2010) Cerebral microbleeds in the elderly: a pathological analysis. Stroke 41:2782-2785. doi: 10.1161/strokeaha.110.593657

9. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, Hartung HP (1999) Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol 20:637-642

10. Yakushiji Y, Nishiyama M, Yakushiji S, Hirotsu T, Uchino A, Nakajima J, Eriguchi M, Nanri Y, Hara M, Horikawa E, Kuroda Y (2008) Brain microbleeds and global cognitive function in adults without neurological disorder. Stroke 39:3323-3328

11. Seo SW, Hwa Lee B, Kim EJ, Chin J, Sun Cho Y, Yoon U, Na DL (2007) Clinical significance of microbleeds in subcortical vascular dementia. Stroke 38:1949-1951. doi: 10.1161/strokeaha.106.477315

12. Zhang M, Chen M, Wang Q, Yun W, Zhang Z, Yin Q, Huang Q, Zhu W (2013) Relationship between cerebral microbleeds and cognitive function in lacunar infarct. J Int Med Res 41:347-355. doi: 10.1177/0300060513476448

13. Liem MK, Lesnik Oberstein SA, Haan J, van der Neut IL, Ferrari MD, van Buchem MA, Middelkoop HA, van der Grond J (2009) MRI correlates of cognitive decline in CADASIL: a 7-year follow-up study. Neurology 72:143-148. doi: 10.1212/01.wnl.0000339038.65508.96

14. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181-184

15. Kang Y, Na D Seoul Neuropsychological Screening Battery. 2003 Incheon. Republic of Korea Human Brain Research & Consulting Corp

16. Kim H, Na DL (1999) BRIEF REPORT Normative Data on the Korean Version of the Boston Naming Test. Journal of Clinical and Experimental Neuropsychology 21:127-133

17. Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, Mollenhauer B, Adler CH, Marder K, Williams-Gray CH, Aarsland D, Kulisevsky J, Rodriguez-Oroz MC, Burn DJ, Barker RA, Emre M (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 27:349-356. doi: 10.1002/mds.24893

18. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, Goldman J, Goetz C, Korczyn A, Lees A, Levy R, Litvan I, McKeith I, Olanow W, Poewe W, Quinn N, Sampaio C, Tolosa E, Dubois B (2007) Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 22:1689-1707; quiz 1837. doi: 10.1002/mds.21507

19. Fahn S, Elton R Members of the UPDRS Development Committee Unified Parkinson's Disease rating scale (1987) Recent developments in Parkinson's disease. Fahn SMC, Colne DB, Goldstein (eds) Florham Park NY Mac Millan Health care Information:153-163

20. Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, Krestin GP, Breteler MM (2008) Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology 70:1208-1214. doi: 10.1212/01.wnl.0000307750.41970.d9

21. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, Wallin A, Ader H, Leys D, Pantoni L, Pasquier F, Erkinjuntti T, Scheltens P (2001) A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 32:1318-1322

22. Poels MM, Ikram MA, van der Lugt A, Hofman A, Krestin GP, Breteler MM, Vernooij MW (2011) Incidence of cerebral microbleeds in the general population: the Rotterdam Scan Study. Stroke 42:656-661. doi: 10.1161/strokeaha.110.607184

23. Vinters HV (1987) Cerebral amyloid angiopathy. A critical review. Stroke 18:311-324

24. Mesker DJ, Poels MM, Ikram MA, Vernooij MW, Hofman A, Vrooman HA, van der Lugt A, Breteler MM (2011) Lobar distribution of cerebral microbleeds: the Rotterdam Scan Study. Arch Neurol 68:656-659. doi: 10.1001/archneurol.2011.93

25. Kim JS, Shim YS, Song IU, Yoo JY, Kim HT, Kim YI, Lee KS (2009) Cardiac sympathetic denervation and its association with cognitive deficits in Parkinson's disease. Parkinsonism Relat Disord 15:706-708. doi: 10.1016/j.parkreldis.2009.01.008

26. Poewe W (2007) Dysautonomia and cognitive dysfunction in Parkinson's disease. Mov Disord 22 Suppl 17:S374-378. doi: 10.1002/mds.21681

27. Kim JS, Oh YS, Lee KS, Kim YI, Yang DW, Goldstein DS (2012) Association of cognitive dysfunction with neurocirculatory abnormalities in early Parkinson disease. Neurology 79:1323-1331. doi: 10.1212/WNL.0b013e31826c1acd

28. Kato H, Izumiyama M, Izumiyama K, Takahashi A, Itoyama Y (2002) Silent cerebral microbleeds on T2*-weighted MRI: correlation with stroke subtype, stroke recurrence, and leukoaraiosis. Stroke 33:1536-1540

29. Koennecke HC (2006) Cerebral microbleeds on MRI: prevalence, associations, and potential clinical implications. Neurology 66:165-171. doi: 10.1212/01.wnl.0000194266.55694.1e

30. Yamada S, Saiki M, Satow T, Fukuda A, Ito M, Minami S, Miyamoto S (2012) Periventricular and deep white matter leukoaraiosis have a closer association with cerebral microbleeds than age. European Journal Of Neurology: The Official Journal Of The European Federation Of Neurological Societies 19:98-104. doi: 10.1111/j.1468-1331.2011.03451.x

31. Sullivan P, Pary R, Telang F, Rifai AH, Zubenko GS (1990) Risk factors for white matter changes detected by magnetic resonance imaging in the elderly. Stroke 21:1424-1428

32. de Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J, Breteler MM (2002) Hypertension and cerebral white matter lesions in a prospective cohort study. Brain 125:765-772

33. Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, Whalley LJ (2005) Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people. Radiology 237:251-257. doi: 10.1148/radiol.2371041496

34. Lee SJ, Kim JS, Yoo JY, Song IU, Kim BS, Jung SL, Yang DW, Kim YI, Jeong DS, Lee KS (2010) Influence of white matter hyperintensities on the cognition of patients with Parkinson disease. Alzheimer Dis Assoc Disord 24:227-233. doi: 10.1097/WAD.0b013e3181d71a13

35. Lee PH, Kim HS, Lee JE, Choi Y, Hong JY, Nam HS, Sohn YH, Kim HO (2011) Comparison of endothelial progenitor cells in Parkinson's disease patients treated with levodopa and levodopa/COMT inhibitor. PLoS One 6:e21536. doi: 10.1371/journal.pone.0021536

36. Rouhl RP, van Oostenbrugge RJ, Damoiseaux J, Tervaert JW, Lodder J (2008) Endothelial progenitor cell research in stroke: a potential shift in pathophysiological and therapeutical concepts. Stroke 39:2158-2165. doi: 10.1161/strokeaha.107.507251

37. Jickling G, Salam A, Mohammad A, Hussain MS, Scozzafava J, Nasser AM, Jeerakathil T, Shuaib A, Camicioli R (2009) Circulating endothelial progenitor cells and age-related white matter changes. Stroke 40:3191-3196. doi: 10.1161/strokeaha.109.554527

38. Young VG, Halliday GM, Kril JJ (2008) Neuropathologic correlates of white matter hyperintensities. Neurology 71:804-811. doi: 10.1212/01.wnl.0000319691.50117.54

39. Koennecke H (2006) Cerebral microbleeds on MRI: prevalence, associations, and potential clinical implications. Neurology 66:165-171

40. Bartels AL, van Berckel BN, Lubberink M, Luurtsema G, Lammertsma AA, Leenders KL (2008) Blood-brain barrier P-glycoprotein function is not impaired in early Parkinson's disease. Parkinsonism Relat Disord 14:505-508. doi: 10.1016/j.parkreldis.2007.11.007

41. Bartels AL, Kortekaas R, Bart J, Willemsen AT, de Klerk OL, de Vries JJ, van Oostrom JC, Leenders KL (2009) Blood-brain barrier P-glycoprotein function decreases in specific brain regions with aging: a possible role in progressive neurodegeneration. Neurobiol Aging 30:1818-1824. doi: 10.1016/j.neurobiolaging.2008.02.002

42. Mok V, Srikanth V, Xiong Y, Phan TG, Moran C, Chu S, Zhao Q, Chu WW, Wong A, Hong Z, Liu X, Wong LK, Ding D (2014) Race-ethnicity and cerebral small vessel disease - Comparison between Chinese and White populations. Int J Stroke. doi: 10.1111/ijs.12270

43. Feigin VL, Lawes CM, Bennett DA, Anderson CS (2003) Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2:43-53

44. Cordonnier C, van der Flier WM, Sluimer JD, Leys D, Barkhof F, Scheltens P (2006) Prevalence and severity of microbleeds in a memory clinic setting. Neurology 66:1356-1360. doi: 10.1212/01.wnl.0000210535.20297.ae

45. Kwa VI, Franke CL, Verbeeten B, Jr., Stam J (1998) Silent intracerebral microhemorrhages in patients with ischemic stroke. Amsterdam Vascular Medicine Group. Ann Neurol 44:372-377. doi: 10.1002/ana.410440313

46. Werring DJ, Frazer DW, Coward LJ, Losseff NA, Watt H, Cipolotti L, Brown MM, Jager HR (2004) Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. Brain 127:2265-2275. doi: 10.1093/brain/awh253

47. Patel B, Lawrence AJ, Chung AW, Rich P, Mackinnon AD, Morris RG, Barrick TR, Markus HS (2013) Cerebral microbleeds and cognition in patients with symptomatic small vessel disease. Stroke 44:356-361. doi: 10.1161/strokeaha.112.670216

48. Benedictus MR, Goos JD, Binnewijzend MA, Muller M, Barkhof F, Scheltens P, Prins ND, van der Flier WM (2013) Specific risk factors for microbleeds and white matter hyperintensities in Alzheimer's disease. Neurobiol Aging. doi: 10.1016/j.neurobiolaging.2013.04.023

49. Klinkenberg I, Sambeth A, Blokland A (2011) Acetylcholine and attention. Behavioural brain research 221:430-442

50. Jeerakathil T, Wolf PA, Beiser A, Hald JK, Au R, Kase CS, Massaro JM, DeCarli C (2004) Cerebral microbleeds: prevalence and associations with cardiovascular risk factors in the Framingham Study. Stroke 35:1831-1835. doi: 10.1161/01.STR.0000131809.35202.1b

51. Lee SH, Bae HJ, Ko SB, Kim H, Yoon BW, Roh JK (2004) Comparative analysis of the spatial distribution and severity of cerebral microbleeds and old lacunes. J Neurol Neurosurg Psychiatry 75:423-427

ABSTRACT (IN KOREAN)

파킨슨 병 환자에서 인지 기능에 대한 뇌 미세출혈의 영향

<지도교수 이지용>

연세대학교 대학원 의학과

함 지 현

뇌 미세출혈은 노인들이나 다양한 질병에서 인지 손상과 연관되어 있다고 알려져 있으나, 파킨슨병에서는 아직 연구에 의해 증명되지 않고 있다. 본 연구에서 저자는 파킨슨병 환자를 대상으로 인지 상태에 따라 뇌 미세출혈의 발생 정도를 분석하였으며 인지 기능에 뇌 미세출혈이 영향을 미치는지도 연구하였다. 파킨슨 치매 36명, 파킨슨 경도 인지 장애 46명, 인지 기능이 정상인 파킨슨병 환자 41명 그리고 대조군 49명의 뇌 미세출혈을 T2-강조 기울기회복에코 영상을 이용하여 분석하였으며, 더 나아가 뇌 미세출혈의 유무와 인지 서브도메인과의 관계를 분석하기 위해 세부적인 신경인지검사를 시행하였다. 뇌 미세출혈은 파킨슨 치매 환자에서 36.1%로 다른 파킨슨 환자 및 대조군에 비하여 유의하게 자주 발생하는 결과를 보였다.(파킨슨 경도 인지 장애(15.2%), 인지 기능이 정상인 파킨슨병 환자(14.6%), 대조군(12.2%, p=0.025)). 그러나 파킨슨 치매와 뇌 미세출혈의 연관성은 공변량으로 백질변성을 보정한 후에는 유의한 결과를 보이지 않았으며 해부학적 위치에

따라, 심부, 엽상, 천막하에서 네 군간의 차이 또한 보이지 않았다.
파킨슨병에서 뇌 미세출혈의 인지에 대한 영향을 분석하기 위해 나이, 성별, 교육정도 그리고 백질 변성 정도를 보정하였으며 그 결과, 뇌 미세출혈을 동반한 파킨슨병 환자가 뇌 미세출혈이 동반되지 않은 파킨슨병 환자에 비하여 주의집중력 도메인에서 저하된 소견을 확인하였다.(34.9 vs 42.6, p=0.018). 본 연구의 결과는 비록 뇌 미세출혈이 백질 변성의 정도와 밀접한 관련이 있지만 파킨슨 치매 환자에서 더 흔하게 발견될 수 있다는 것을 보여주고 있으며, 더 나아가 뇌 미세출혈의 존재가 파킨슨병에서 인지 기능을 악화시키는데 중요한 역할을 할 수 있다는 증거가 될 수 있다.

핵심되는 말 : 뇌 미세출혈, 파킨슨병, 인지수행력