

Open Access

Medial Temporal Atrophy and Memory Dysfunction in Poststroke Cognitive Impairment-No Dementia

Beom Joon Kim,^{a,b} Mi-Young Oh,^a Myung Suk Jang,^b Moon-Ku Han,^b Jisung Lee,^c Juneyoung Lee,^c Yeonwook Kang,^d Kyung-Ho Yu,^e Byung-Chul Lee,^e Sangyun Kim,^b Byung-Woo Yoon,^a Hee-Joon Bae^b

^aDepartment of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

^bDepartment of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

^cDepartment of Biostatistics, Korea University College of Medicine, Seoul, Korea

^dDepartment of Psychology, Hallym University, Chuncheon, Korea

^eDepartment of Neurology, Hallym University College of Medicine, Chuncheon, Korea

Background and Purpose It was recently reported that the prevalence of poststroke memory dysfunction might be higher than previously thought. Stroke may exist concomitantly with underlying Alzheimer's disease (AD), and so we determined whether post-stroke memory dysfunction indicates manifestation of underlying subclinical AD.

Methods Of 1201 patients in a prospective cognitive assessment database, we enrolled subjects with poststroke amnesic vascular cognitive impairment-no dementia (aVCIND; $n=48$), poststroke nonamnesic vascular cognitive impairment-no dementia (naVCIND; $n=50$), and nonstroke amnesic mild cognitive impairment (aMCI; $n=65$). All subjects had cognitive deficits, but did not meet the criteria for dementia. A standardized neuropsychological test battery and magnetic resonance imaging were performed at least 90 days after the index stroke (mean, 473 days). Visual assessment of medial temporal atrophy (MTA) was used as a measure of underlying AD pathology.

Results The MTA score was significantly lower in the naVCIND group (0.64 ± 0.85 , mean \pm SD) than in the aVCIND (1.10 ± 1.08) and aMCI (1.45 ± 1.13 ; $p < 0.01$) groups. Multivariable ordinal logistic regression analysis revealed that compared with naVCIND, aVCIND [odds ratio (OR)=2.69; 95% confidence interval (CI)=1.21-5.99] and aMCI (OR=5.20; 95% CI=2.41-11.23) were significantly associated with increasing severity of MTA.

Conclusions Our findings show that compared with poststroke naVCIND, the odds of having more-severe MTA were increased for poststroke aVCIND and nonstroke aMCI.

J Clin Neurol 2012;8:43-50

Key Words vascular cognitive impairment, memory dysfunction, stroke, poststroke dementia.

Received April 29, 2011
Revised July 18, 2011
Accepted July 18, 2011

Correspondence

Hee-Joon Bae, MD, PhD
Department of Neurology,
Seoul National University
Bundang Hospital, 82 Gumi-ro
173beon-gil, Bundang-gu,
Seongnam 463-707, Korea
Tel +82-31-787-7464
Fax +82-31-787-4059
E-mail braindoc@snu.ac.kr

Introduction

It is being increasingly recognized that the prevalence of vascular cognitive impairment (VCI) is higher than originally thought. Since VCI is considered to develop under the influence of various cardiovascular risk factors, it is emerging as a potentially treatable and preventable form of dementing disorders.¹

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

However, currently available therapeutic options for treatment of dementia, such as cholinesterase inhibitors, were originally devised for Alzheimer's disease (AD), and their application in vascular dementia (VaD) has produced limited and uncertain clinical benefit.²

It is widely recognized that at the incipient stage, AD patients generally complain about memory problems, whereas VaD patients usually present with cognitive deficits involving nonmemory domains.³ However, a substantial proportion of stroke survivors suffer from poststroke memory dysfunction, and several factors, including medial temporal atrophy (MTA)

or white matter hyperintensities (WMHs), are associated with poststroke memory dysfunction.⁴ Furthermore, there is increasing evidence that coexisting cerebrovascular disease precipitates and unmasks underlying preclinical AD.⁵ Stroke and AD are highly prevalent and the two conditions share common vascular risk factors, and so it can be hypothesized that patients with poststroke memory dysfunction may have had subclinical AD before their stroke, and their memory deficits may be the divulgence of underlying AD triggered by stroke. This issue has not been studied in populations with cognitive impairment-no dementia (CIND), which is clearly the foremost target of therapeutic interventions for preventing dementia.⁶ We sought to test this hypothesis by measuring the severity of MTA, which is an acknowledged neuroimaging index of AD.⁷ For this purpose, we compared patients with poststroke amnesic vascular cognitive impairment-no dementia (aVCIND) and patients with nonstroke amnesic mild cognitive impairment (aMCI) to patients with poststroke nonamnesic vascular cognitive impairment-no dementia (naVCIND).

Methods

Subject recruitment

This was a retrospective analysis based on a prospective cognitive test database. The patient selection process is summarized in Fig. 1. A battery of standard neuropsychological tests was administered to 1201 patients at Seoul National University Bundang Hospital between May 2007 and March 2009. Of these 1201 patients, 396 had a documented history of clinical stroke with which neuroimaging findings were compatible; the remaining 805 patients were designated as nonstroke subjects. Stroke was defined using the World Health Organization def-

inition of “rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular origin”.⁸ CIND was defined as having cognitive impairment but not meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for dementia.^{6,9} We also applied an Instrumental Activity of Daily Living score of <0.43 as indicating “no dementia”.¹⁰

For poststroke patients, a standardized neuropsychological battery was administered at least 90 days after stroke onset. The interval from stroke onset to neuropsychological evaluation was 473±311 days (mean±SD). We selected poststroke VCIND patients (*n*=156) who had an impairment in one or more cognitive domains but did not meet the DSM-IV-TR criteria for dementia. Cognitive impairment in language, visuospatial function, or memory domains was defined as a score in the each of the domain-specific tests of less than the 7th percentile (mean-1.5 SD). Cognitive impairment in the frontal domain was determined by a score of less than the 7th percentile in two or more of the five frontal-domain-specific tests (details of the neuropsychological tests used are given below). Poststroke VCIND was further classified into poststroke amnesic VCIND (aVCIND; *n*=71) and poststroke nonamnesic VCIND (naVCIND; *n*=85), according to the presence of memory impairment. Among 805 nonstroke patients, 331 were identified as having CIND; 128 patients who had cognitive impairment in the memory domain were further categorized into the aMCI group. Patients without coronal magnetic resonance imaging (MRI) results were excluded (23 from the aVCIND group, 35 from the naVCIND group, and 63 from the aMCI group). These criteria resulted in 163 patients (48 aVCIND, 50 naVCIND, and 65 aMCI) being included in this study. All of the included

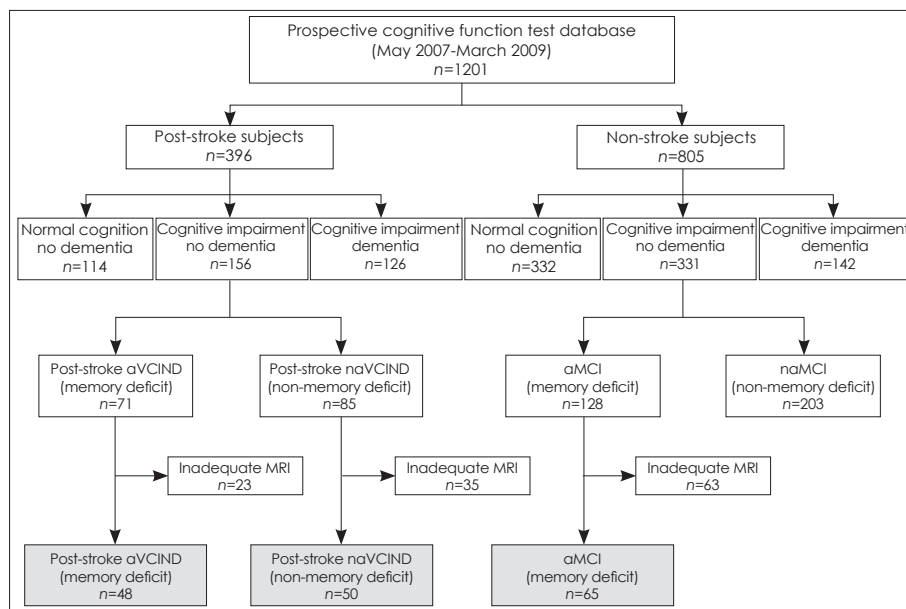


Fig. 1. Recruitment of the study population. Gray boxes denote the enrolled subjects who were included in the final analyses. aVCIND: amnesic vascular cognitive impairment-no dementia, naVCIND: nonamnesic vascular cognitive impairment-no dementia, aMCI: amnesic mild cognitive impairment.

patients were free of any other organic medical or neurological conditions that may adversely affect cognitive functions. The study protocols were approved by the local institutional review board.

Cognitive assessment

A battery of standard neuropsychological tests was adapted from the 60-minute neuropsychology protocol of the Vascular Cognitive Impairment Harmonization Standards (VCIHS).¹¹ The Korean-VCIHS Neuropsychologic Battery was standardized for the Korean population, and its validity and feasibility were examined and confirmed in a multicenter epidemiological study involving 15 hospitals with nationwide coverage.¹² The Korean-VCIHS Neuropsychologic Battery comprises the following cognitive tests of various cognitive domains: frontal executive/activation (animal naming test, phonemic fluency test, Digit Symbol Coding, Trail Making Test), language/lexical retrieval (Korean-Boston Naming Test - short form), visuospatial (Rey-Osterrieth Complex Figure Test: Copy), memory (Seoul Verbal Learning Test), depressive mood (Geriatric Depression Scale), and others (Informant Questionnaire for Cognitive Decline in the Elderly, Korean Mini Mental State Examination, and Instrumental Activity of Daily Living). Trained clinical psychometricians who were blinded to the clinical and radiological profile of each patient administered the battery. The score on each cognitive test was transformed into a standardized Z-score [$Z\text{-score} = (\text{individual score} - \text{population mean score}) / (\text{population SD})$].

Vascular risk factors and MRI evaluation of the patients

The baseline demographic and clinical characteristics of patients included in the study were collected, including age, gender, years of education, handedness, and vascular risk factors, such as presence of hypertension (previous use of antihypertensive medication, systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg), diabetes mellitus (previous use of glucose-lowering medication, fasting blood glucose >7.0 mmol/L, or 2-hours-postprandial blood glucose >11.1 mmol/L), dyslipidemia (previous use of lipid-lowering medication, total cholesterol >6.0 mmol/L, or low-density lipoprotein cholesterol >4.14 mmol/L), and smoking (current smoker or stopped smoking within the past 5 years). For post-stroke patients, the severity of stroke was assessed using the National Institutes of Health Stroke Scale score, which was measured at hospital admission for the most-recent stroke, and the modified Rankin Scale score, measured at discharge from that admission.

All participants underwent brain MRI, and the mean interval between MRI and test for the neuropsychological battery

was 153 days. The MRI studies were performed using a 1.5-tesla superconducting magnet (Intera, Philips Healthcare, Eindhoven, The Netherlands). The standardized MRI protocols consisted of an axial T2-weighted spin echo, coronal T2-weighted spin echo, fluid-attenuated inversion recovery image, gradient-echo image, and axial T1-weighted image. MTA was rated using a 5-point rating scale, as described previously.¹³ Both sides were rated simultaneously, and in the case of noticeable asymmetry, the score of the more affected side was chosen as being representative.¹⁴ WMHs were rated visually using a 10-point rating scale, based on the fluid-attenuated inversion recovery image.¹⁵ Information regarding the subtype, location, and laterality of the stroke and the involvement of the medial temporal lobe was obtained from the prospective stroke registry and by reviewing the electronic medical records and MRI findings. Two reviewers (B.J. Kim and M.-Y. Oh) independently and blindly rated the MTA and WMHs (Spearman's correlation coefficient: 0.79 for MTA and 0.73 for WMHs), and any disagreement was settled by consensus.

Statistical analysis

Differences in baseline characteristic variables among the poststroke aVCIND, poststroke naVCIND, and aMCI groups were examined by using Pearson's χ^2 test, the Kruskal-Wallis test with pairwise Mann-Whitney U test, or one-way analysis of variance with Bonferroni's post-hoc adjustment for multiple comparisons, as appropriate. Z-scores were described as mean \pm SE values. Bivariate analyses and multivariable ordinal logistic regression analyses performed by taking the MTA score as a dependent variable were used to assess whether covariates were associated with an increasing severity of MTA. To build ordinal logistic regression models, three patients with the most-severe MTA (MTA score=4) were combined with the group of patients with an MTA score of 3. The distribution of patients by MTA score used in the model was as follows: 60 (36.8%), 52 (31.9%), 29 (18.0%), and 22 (13.5%) patients with MTA scores of 0, 1, 2, and 3 or 4, respectively. The proportional odds assumption for each ordinal logistic regression model was examined and found to be satisfactory. Variables with a bivariate $p < 0.10$ for their association with MTA were selected for adjustment in multivariate models, including age, WMHs, hypertension, and diabetes. Statistical significance was defined as a probability value of $p \leq 0.05$. All statistical analyses were performed using SPSS 15.0 (SPSS, Chicago, IL, USA).

Results

The distributions of gender and MTA differed significantly among the three CIND groups; however, age, dominant hand, education, WMHs, and cardiovascular risk factors did not dif-

fer (Table 1). Stroke-related features, the location and laterality of stroke lesions, the stroke subtype, and the severity of the stroke did not differ significantly between poststroke aVCIND and naVCIND patients. The MTA score varied significantly among the three types of CIND ($p < 0.01$, Kruskal-Wallis test). Pairwise comparisons revealed that the MTA score was significantly lower in the poststroke naVCIND group (median, interquartile range; 1, 0-2) than in the poststroke aVCIND group (1, 0-1; $p = 0.022$) and the aMCI group (1, 0-2; $p < 0.01$; the significance level was set to $p \leq 0.017$ after adjusting for pairwise comparison). However, the MTA score did not differ between the poststroke aVCIND and aMCI groups ($p = 0.10$).

Analysis of variance showed that with the exception of the memory score, the domain-specific test scores did not differ among the three CIND groups (Table 2) (Fig. 2). The memory domain was used to differentiate poststroke aVCIND from poststroke naVCIND. Global Frontal Function score, obtained by averaging the Z-scores of the five frontal domain-specific tests, did not differ between the groups ($p = 0.94$).

Ordinal logistic regression analyses showed that there was a significant association between the severity of MTA and the type of CIND (Table 3). In multivariable analysis, the odds ratio for poststroke aVCIND was 2.69 (95% confidence interval = 1.21-5.99) and the odds ratio for aMCI was 5.20 (95% con-

Table 1. Comparison of baseline characteristics among the three CIND groups

	Poststroke aVCIND (n=48)	Poststroke naVCIND (n=50)	aMCI (n=65)	p^*
Demographic factors				
Male gender	39 (81.3%)	27 (54.0%)	45 (69.2%)	0.02
Age (years)	66.31±9.99	67.64±9.70	66.63±7.94	0.75
Right-handedness	44 (91.7%)	48 (96.0%)	61 (93.8%)	0.87
Years of education				0.07
0-6 years	11 (22.9%)	18 (36.0%)	12 (18.5%)	
7-12 years	25 (52.1%)	16 (32.0%)	38 (58.5%)	
>13 years	12 (25.0%)	16 (32.0%)	15 (23.1%)	
Cardiovascular risk factors				
Hypertension	32 (66.7%)	32 (64.0%)	47 (72.3%)	0.62
Diabetes	19 (39.6%)	14 (28.0%)	19 (29.2%)	0.39
Hyperlipidemia	24 (50.0%)	20 (40.0%)	22 (33.8%)	0.22
Smoking	24 (50.0%)	22 (44.0%)	37 (56.9%)	0.39
Neuroimaging factors				
WMHs, mean±SD	2.52±1.44	2.52±2.17	3.06±2.10	0.23
MTA score				
0	17 (35.4%)	27 (54.0%)	16 (24.6%)	
1	16 (33.3%)	17 (34.0%)	19 (29.2%)	
2	9 (18.8%)	3 (6.0%)	17 (26.2%)	
3	5 (10.4%)	3 (6.0%)	11 (16.9%)	
4	1 (2.1%)	0 (0%)	2 (3.1%)	
Median (IQR)	1 (0, 2)	0 (0, 1)	1 (0, 2)	<0.01
Stroke-related factors				
Ischemic stroke	42 (87.5%)	48 (96.0%)	-	0.16
Supratentorial stroke	43 (89.6%)	47 (94.0%)	-	0.48
Laterality of stroke				
Left	29 (60.4%)	28 (56.0%)	-	
Right	13 (27.1%)	19 (38.0%)	-	
Bilateral	6 (12.5%)	3 (6.0%)	-	
Involvement of medial temporal lobe	3 (6.3%)	2 (4.0%)	-	0.67
Admission NIHSS score, median (IQR)	2 (1, 4)	2 (1, 6)	-	0.91
Discharge mRS score, median (IQR)	1 (1, 2)	1 (0, 3)	-	0.82

Values are number of patients (percentages) except where indicated otherwise.

*Pearson's Chi-squared test, analysis of variance (ANOVA), Kruskal-Wallis test, or Mann-Whitney's U test, as appropriate.

WMHs: white-matter hyperintensities, CIND: cognitive impairment-no dementia, aVCIND: amnesic vascular cognitive impairment and no dementia, naVCIND: nonamnesic vascular cognitive impairment-no dementia, aMCI: amnesic mild cognitive impairment, MTA: medial temporal atrophy, NIHSS: National Institutes of Health Stroke Scale, IQR: interquartile range, mRS: modified Rankin Scale.

fidence interval=2.41-11.23) relative to poststroke naVCIND. When compared with aMCI, poststroke aVCIND was not significantly associated with the severity of MTA ($p=0.11$). In

addition, age and diabetes mellitus were independently associated with increasing severity of MTA (Table 3).

Table 2. Comparison of cognitive function and other related tests among the three CIND groups

	Poststroke aVCIND (n=48)	Poststroke naVCIND (n=50)	aMCI (n=65)	p^*
Frontal executive and association function				
Animal naming, Z-score	-0.92±0.15	-0.67±0.14	-0.84±0.15	0.51
COWAT, phonemic, Z-score	-0.57±0.17	-0.48±0.17	-0.69±0.16	0.66
Digit symbol coding, Z-score	-0.97±0.17	-0.73±0.16	-0.87±0.13	0.55
Trail making test - A, Z-score	-0.90±0.19	-1.87±0.48	-1.38±0.26	0.14
Trail making test - B, Z-score	-1.55±0.36	-0.66±0.30	-0.83±0.20	0.08
Global frontal function, Z-score	-0.99±0.15	-0.91±0.15	-0.96±0.13	0.94
Language/lexical retrieval				
Boston naming test, Z-score	-0.82±0.28	-0.68±0.26	-1.12±0.20	0.41
Visuospatial function				
RCFT score, Z-score	-1.36±0.24	-1.34±0.26	-1.41±0.19	0.97
Memory function				
HVLT-R, delayed recall, Z-score	-2.31±0.13†	-0.23±0.11	-2.28±0.11†	<0.01
Global cognitive function				
MMSE, raw score	25.02±0.41	25.70±0.52	24.88±0.49	0.45
MMSE, Z-score	-0.74±0.14	-0.28±0.12	-0.70±0.16	0.06
Other functional assessments				
IADL, raw score	0.12±0.02	0.09±0.01	0.13±0.02	0.24
IQCODE, raw score	3.36±0.04	3.40±0.05	3.40±0.03	0.78
Geriatric Depression Scale, raw score	11.81±1.10	12.26±1.01	13.45±0.82	0.44

Each score is the mean±SE value.

*ANOVA, †Significant difference from poststroke naVCIND in multiple comparisons with Bonferroni's post-hoc adjustment.

aMCI: amnesic mild cognitive impairment, aVCIND: amnesic vascular cognitive impairment and no dementia, naVCIND: nonamnesic vascular cognitive impairment-no dementia, CIND: cognitive impairment-no dementia, COWAT: Controlled Oral Word Association Test, HVLT-R: Hopkins Verbal Learning Test-Revised, IADL: Instrumental Activity of Daily Living, IQCODE: Informant Questionnaire for Cognitive Decline in the Elderly, MMSE: Mini-Mental Status Examination, RCFT: Rey-Osterrieth Complex Figure Test.

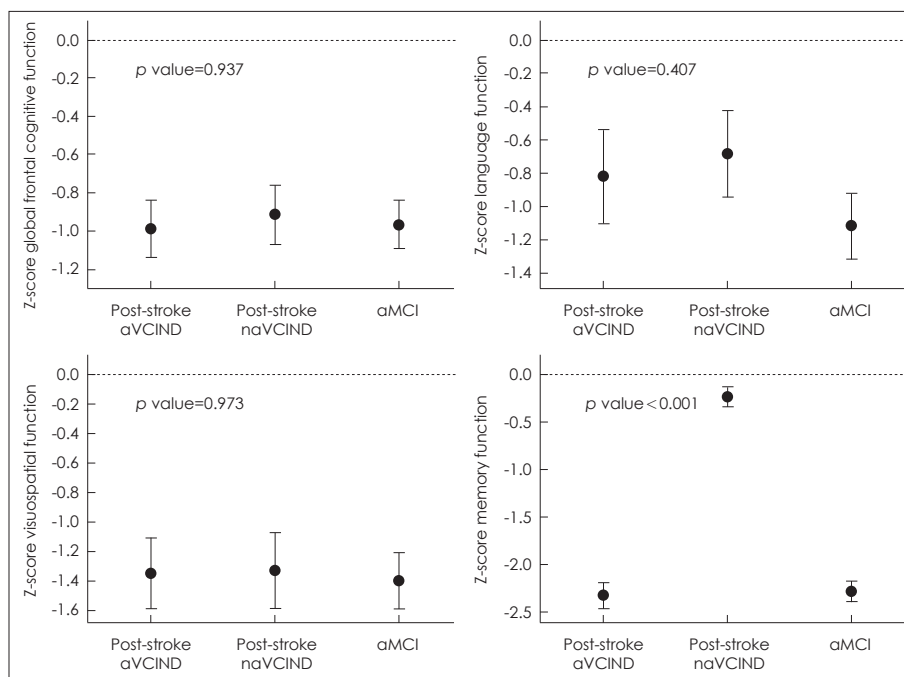


Fig. 2. Comparison of Z-scores among the three vascular cognitive impairment and no dementia (CIND) groups. aMCI: amnesic mild cognitive impairment, aVCIND: amnesic vascular cognitive impairment-no dementia, naVCIND: non-amnesic vascular cognitive impairment-no dementia.

Table 3. Results from univariate and multivariate ordinal logistic regression analyses for the increasing severity of MTA

	Univariate OR (95% CI)	Multivariable OR [†] (95% CI)
Demographic factors		
Male gender	0.99 (0.55-1.80)	-
Age (per 1-year increase)	1.09 (1.05-1.13)	1.10 (1.06-1.14)
Right-handedness	0.77 (0.24-2.43)	-
Years of education		
0-6 years	1.00 (reference)	-
7-12 years	1.25 (0.57-2.73)	
>13 years	1.22 (0.61-2.42)	
Neuroimaging factors		
Types of CIND		
Poststroke aVCIND	2.35 (1.11-4.96)	2.69 (1.21-5.99)
aMCI	4.23 (2.08-8.63)	5.20 (2.41-11.23)
Poststroke naVCIND	1.00 (reference)	1.00 (reference)
WMHs (0-9 scale) (per 1-grade increase)	1.33 (1.15-1.55)	1.14 (0.96-1.34)
Cardiovascular risk factors		
Hypertension	2.02 (1.09-3.74)	1.69 (0.85-3.34)
Diabetes	2.48 (1.35-4.56)	2.01 (1.05-3.86)
Hyperlipidemia	0.93 (0.53-1.64)	-
Smoking	1.15 (0.66-2.02)	-
Stroke-related factors*		
Ischemic stroke	1.67 (0.41-6.80)	-
Supratentorial stroke	0.61 (0.16-2.29)	-
Location of stroke		
Left	0.77 (0.34-1.71)	-
Bilateral	1.21 (0.31-4.70)	-
Right	1.00 (reference)	-
Stroke involving medial temporal lobe	2.44 (0.48-12.45)	-
Admission NIHSS score (per 1-point increase)	1.03 (0.92-1.15)	-
Discharge mRS score (per 1-point increase)	1.16 (0.87-1.56)	-

Univariate or multivariable ordinal logistic regression analyses were performed by taking the MTA score as a dependent variable.

*Univariate ORs of stroke-related factors were calculated based on patients with poststroke aVCIND and naVCIND, excluding the nonstroke aMCI group, [†]A multivariable model was constructed using variables with $p < 0.10$ in univariate analyses.

aMCI: amnesic mild cognitive impairment, aVCIND: amnesic vascular cognitive impairment-no dementia, CI: confidence interval, CIND: cognitive impairment-no dementia, MTA: medial temporal atrophy, naVCIND: nonamnesic vascular cognitive impairment-no dementia, OR: odds ratio, WMHs: white-matter hyperintensities.

Discussion

The patients in this study were divided into two groups according to the presence of memory dysfunction so as to make it possible to evaluate the association between MTA and memory dysfunction in patients with poststroke CIND. The effect of stroke was evaluated by comparing nonstroke aMCI patients with poststroke CIND patients. With the exception of memory, patients in the three CIND groups defined in our study had similar cognition and functional ability profiles. We found that the odds of having more-severe MTA were increased for poststroke aVCIND and nonstroke aMCI relative to poststroke naVCIND. Older age and diabetes mellitus were also found to be independently associated with MTA.

The concept of poststroke memory dysfunction seems counterintuitive in that stroke does not usually affect the memory-processing structures.¹⁶ However, one-third to one-half of stroke survivors were reported to have memory dysfunction around 3 months after the stroke,⁴ and the risk of dementia doubles with a history of stroke.¹⁷ Both MTA and imaging markers of cerebrovascular disease are useful in predicting the development of clinical dementia.¹⁸ Experimental studies have also suggested that certain mechanisms are responsible for progressive memory deterioration. Decreased cerebral blood flow, which occurs with ischemic stroke, may modulate trafficking of β -amyloid between the blood and the brain, resulting in the attenuation of β -amyloid clearance from the brain.^{19,20} Moreover, small ischemic injuries that develop in the paraven-

tricular area and deep structures may cause widespread disconnection of cholinergic innervations to the cortex,^{21,22} thereby inducing additive attrition of cognitive reserve.²³

We deliberately recruited CIND patients from our large population of patients with neuropsychological assessments. Cholinesterase inhibitors and memantine, which are used to treat AD patients, seem to provide little benefit to VaD patients,² and there has been no clinical trial regarding their efficacy in the treatment of poststroke dementia. According to DSM-IV-TR criteria, the presence of stroke per se in a demented individual excludes a diagnosis of AD. However, our results, as well as those from other recent studies, show that VaD patients usually have “mixed” pathology.^{24,25} In this context, our findings suggest that poststroke CIND can be regarded as subclinical AD if there is MTA or memory dysfunction, and that cholinesterase inhibitors or memantine can be beneficial for these individuals. In addition, the consideration of MTA when recruiting subjects for VCI trials or in secondary analysis of VCIND research would improve the homogeneity of study populations.

The association between MTA and poststroke dementia has been addressed by previous studies. However, the clinical implications of the results obtained in those studies were limited because they disregarded CIND or were case series of stroke at a specific location.²⁶⁻²⁹ In addition to the type of CIND, our study detected increases in the severity of MTA with the presence of diabetes, which is consistent with a previous report.³⁰ WMHs and hypertension were not associated with severity of MTA in multivariable analyses, in spite of their significance in univariate analyses (Table 3). A lack of power due to the small sample is a possible explanation for this finding. Furthermore, previous studies also found that the association between WMHs and MTA is controversial.^{31,32} Contrary to the concept of early executive dysfunction in VaD, frontal function did not differ among the three CIND groups in the present study. However, the development of executive dysfunction has been reported to be as common in AD as in VaD.³³

There are several reasons why our results should be interpreted with caution. First, this study was conducted at a single center, had a cross-sectional design, and a relatively small sample. Second, it should be noted that approximately 5% of MCI patients are reported to return to normal over time and that the natural course of progressive memory deterioration is thought to be dynamic.^{4,34} Third, single- and multidomain CINDs were not distinguished in our study due to the small sample. Fourth, the visual rating scale of MTA was used instead of a volumetric assessment. However, volumetry is cumbersome because it requires expensive software and a time-consuming rendering process, which limits its usefulness for research purposes. Moreover, it has been reported that visual and volumetric assessments of MTA are equally accurate.^{35,36} Fifth, prestroke

neuropsychological assessments were not available for our subjects.

Our results do not indicate that poststroke memory dysfunction is essentially AD or that such patients should receive cholinesterase inhibitors - only a prospective cohort study with an adequate duration of follow-up can clarify the association between AD and poststroke memory dysfunction. Considering the increasing burden of stroke and dynamic interrelationships among vascular etiologies, degenerative changes in the brain, and host factors with respect to VCI,^{37,38} our findings support the notion that a stroke event may trigger subclinical AD-type neurodegeneration and result in poststroke memory dysfunction.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgements

This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health, Welfare & Family Affairs, Republic of Korea (A102065). The funding organization did not participate in the design, conduct, or analysis of the study, or in the preparation of this report.

REFERENCES

- Hachinski V. The 2005 Thomas Willis Lecture: stroke and vascular cognitive impairment: a transdisciplinary, translational and transactional approach. *Stroke* 2007;38:1396.
- Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurol* 2007;6:782-792.
- Traykov L, Baudic S, Thibaudet MC, Rigaud AS, Smagghe A, Boller F. Neuropsychological deficit in early subcortical vascular dementia: comparison to Alzheimer's disease. *Dement Geriatr Cogn Disord* 2002; 14:26-32.
- Snaphaan L, de Leeuw FE. Poststroke memory function in nondemented patients: a systematic review on frequency and neuroimaging correlates. *Stroke* 2007;38:198-203.
- Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. *Neurobiol Aging* 2000;21:321-330.
- Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. *Neurology* 2000;54:447-451.
- Korf ES, Wahlund LO, Visser PJ, Scheltens P. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. *Neurology* 2004;63:94-100.
- The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol* 1988;41:105-114.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*. 4th ed, text revision. Washington, DC: American Psychiatric Association, 2000.
- Kang SJ, Choi SH, Lee BH, Kwon JC, Na DL, Han SH; Korean Dementia Research Group. The reliability and validity of the Korean instrumental activities of daily living (K-IADL). *J Korean Neurol Assoc* 2002;20:8-14.
- Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL,

- Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* 2006;37:2220-2241.
12. Kang Y. Recent developments in the Korean VCI neuropsychology harmonization efforts. *The 4th Congress of the International Society for Vascular Behavioural and Cognitive Disorders (VAS-COG)*. Singapore: 2009.
 13. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 1992;55:967-972.
 14. Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *J Neurol* 1995;242:557-560.
 15. Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA* 2002;288:67-74.
 16. Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, et al. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science* 1998;281:1188-1191.
 17. Savva GM, Stephan BC; Alzheimer's Society Vascular Dementia Systematic Review Group. Epidemiological studies of the effect of stroke on incident dementia: a systematic review. *Stroke* 2010;41:e41-e46.
 18. Staekenborg SS, Koedam EL, Henneman WJ, Stokman P, Barkhof F, Scheltens P, et al. Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. *Stroke* 2009;40:1269-1274.
 19. Niwa K, Kazama K, Younkin L, Younkin SG, Carlson GA, Iadecola C. Cerebrovascular autoregulation is profoundly impaired in mice overexpressing amyloid precursor protein. *Am J Physiol Heart Circ Physiol* 2002;283:H315-H323.
 20. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 2004;5:347-360.
 21. Selden NR, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. *Brain* 1998;121:2249-2257.
 22. Román GC, Kalaria RN. Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia. *Neurobiol Aging* 2006;27:1769-1785.
 23. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol* 2004;3:343-353.
 24. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? *Neurology* 2009;72:368-374.
 25. Zekry D. Is it possible to treat vascular dementia? *Front Neurol Neurosci* 2009;24:95-106.
 26. Hénon H, Pasquier F, Durieu I, Pruvo JP, Leys D. Medial temporal lobe atrophy in stroke patients: relation to pre-existing dementia. *J Neurol Neurosurg Psychiatry* 1998;65:641-647.
 27. Pohjasvaara T, Mäntylä R, Salonen O, Aronen HJ, Ylikoski R, Hietanen M, et al. MRI correlates of dementia after first clinical ischemic stroke. *J Neurol Sci* 2000;181:111-117.
 28. Jokinen H, Kalska H, Ylikoski R, Hietanen M, Mäntylä R, Pohjasvaara T, et al. Medial temporal lobe atrophy and memory deficits in elderly stroke patients. *Eur J Neurol* 2004;11:825-832.
 29. Van der Werf YD, Scheltens P, Lindeboom J, Witter MP, Uylings HB, Jolles J. Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. *Neuropsychologia* 2003;41:1330-1344.
 30. den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia* 2003;46:1604-1610.
 31. van de Pol LA, Verhey F, Frisoni GB, Tsolaki M, Papapostolou P, Nobili F, et al. White matter hyperintensities and medial temporal lobe atrophy in clinical subtypes of mild cognitive impairment: the DESCRIPA study. *J Neurol Neurosurg Psychiatry* 2009;80:1069-1074.
 32. Appel J, Potter E, Bhatia N, Shen Q, Zhao W, Greig MT, et al. Association of white matter hyperintensity measurements on brain MR imaging with cognitive status, medial temporal atrophy, and cardiovascular risk factors. *AJNR Am J Neuroradiol* 2009;30:1870-1876.
 33. Moorhouse P, Song X, Rockwood K, Black S, Kertesz A, Gauthier S, et al. Executive dysfunction in vascular cognitive impairment in the consortium to investigate vascular impairment of cognition study. *J Neurol Sci* 2010;288:142-146.
 34. Kelley BJ, Petersen RC. Mild cognitive impairment. In: Miller BL, Boeve BF. *The behavioral neurology of dementia*. New York: Cambridge University Press, 2009;172-187.
 35. Wahlund LO, Julin P, Johansson SE, Scheltens P. Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: a comparative study. *J Neurol Neurosurg Psychiatry* 2000;69:630-635.
 36. DeCarli C, Frisoni GB, Clark CM, Harvey D, Grundman M, Petersen RC, et al. Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Arch Neurol* 2007;64:108-115.
 37. Erkinjuntti T, Inzitari D, Pantoni L, Wallin A, Scheltens P, Rockwood K, et al. Limitations of clinical criteria for the diagnosis of vascular dementia in clinical trials. Is a focus on subcortical vascular dementia a solution? *Ann N Y Acad Sci* 2000;903:262-272.
 38. Hong KS, Kim J, Cho YJ, Seo SY, Hwang SI, Kim SC, et al. Burden of ischemic stroke in Korea: analysis of disability-adjusted life years lost. *J Clin Neurol* 2011;7:77-84.