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Clinical impact of cerebral microbleeds on cognition in patients with CADASIL

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Abstract Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is inherited microangiopathy caused by mutations in the Notch3 gene. Typical findings from brain magnetic resonance imaging (MRI) include subcortical lacunes, extensive white matter change and cerebral microbleeds (CMBs). CMBs are indicative of bleeding-prone microangiopathy. Despite some studies investigating the association between lacunes and cognitive dysfunction in CADASIL, few studies have examined the relationship between cognitive dysfunction and CMBs. We sought to assess whether CMBs are associated with cognitive dysfunction in CADASIL. This study enrolled 83 consecutive patients with CADASIL between April 2012 and January 2014. Their degree of cognitive dysfunction was assessed by the Korean version of the CERAD neuropsychological assessment battery, digit span test, and the Stroop test. A 3.0-T MRI was used to obtain T1-weighted, fluid-attenuated inversion recovery, and susceptibility weighted images. In multiple logistic regression analysis, the grade of CMBs influenced tests of memory dysfunction ($p=0.003$). Three or more lacunes correlated with dysfunction in the executive domain ($p=0.013$) and attention domain ($p=0.005$). White matter hyperintensity (WMH) was an independent predictor of executive dysfunction ($p=0.001$). These findings suggest that in addition to lacunes, CMBs and WMHs may be useful imaging markers to associated with cognitive dysfunction in CADASIL.

Key words: Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Hypertension, Lacunar infarct, Cognition

INTRODUCTION

Cerebral microbleeds (CMBs) are the perivascular collections of hemosiderin deposits caused by tiny extravasations of blood.[1,2] They can easily be detected by Magnetic Resonance Imaging (MRI) due to recent advances in MRI technology.[1,2] Susceptibility-weighted images (SWIs) are high-resolution 3D T2 sequences uniquely attenuated to the detection of hemorrhage.[3] The SWI method and smaller section thicknesses are known to be associated with higher rates of CMB detection, especially CMBs on the lobar lesion.[4] CMBs are frequently detected in patients with ischemic stroke as well as those with intracranial hemorrhage (ICH) in cerebral small vessel disease, which suggests that patients with cerebral small vessel disease have ischemia and CMBs comorbidities.[5] Also, previous reports have shown that the presence of CMBs predicts the recurrence of ischemic stroke.[6]

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a well known inherited cerebral small vessel disease caused by mutations in the Notch3 gene.[7] The main clinical manifestations are a recurrent stroke, cognitive decline, chronic headache, mood disturbances, and seizure.[8,9] Differences between Caucasian and Asian CADASIL patients concerning neuroimaging features include higher rates of

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ICH in East Asians.[10] ICH has rarely been described in Caucasian patients with CADASIL.[11] Despite some studies investigating the association between lacunes and cognitive dysfunction in CADASIL, few studies have examined the relationship between cognitive dysfunction and CMBs. We are aware of only one prior study that found a longitudinal association between CMBs and cognition.[12] Therefore, we sought to assess whether CMBs are associated with cognitive dysfunction in patients with CADASIL.

Table 1. Demographic characteristics (n = 83)

Age, year	62.5 ± 12.5
Male sex	48 (57.8%)
Education, year	9.5 ± 5.4
Hypertension	49 (59.0%)
Diabetes Mellitus	12 (14.5%)
Hypercholesterolemia	19 (22.9%)
Ever-smoking	34 (41.0%)
Number of lacunes, median (range)	3.0 (0-22)
Number of CMBs, median (range)	3.0 (0-120)
Scheltens scores	28.4 ± 13.6

CMBs = cerebral microbleeds. Values are mean ± SD.

MATERIALS AND METHODS

The subjects for this study include consecutive patients who had been diagnosed with CADASIL by genetic testing or skin biopsy analysis at Jeju National University Hospital's Neurology Department between April 2012 and January 2014. We enrolled 86 patients with CADASIL. Patients who did not undergo a MRI examination prospectively (n = 2) or a comprehensive neuropsychological evaluation (n = 1) were excluded. Therefore, finally, 83 patients were enrolled.

Data for our analyses were derived from previously reported our study. The details of the study method for this article have been described in detail elsewhere.[13]

All statistical analyses were performed using SPSS 21.0 (IBM, Armonk, NY, USA). CMBs were classified as ab-

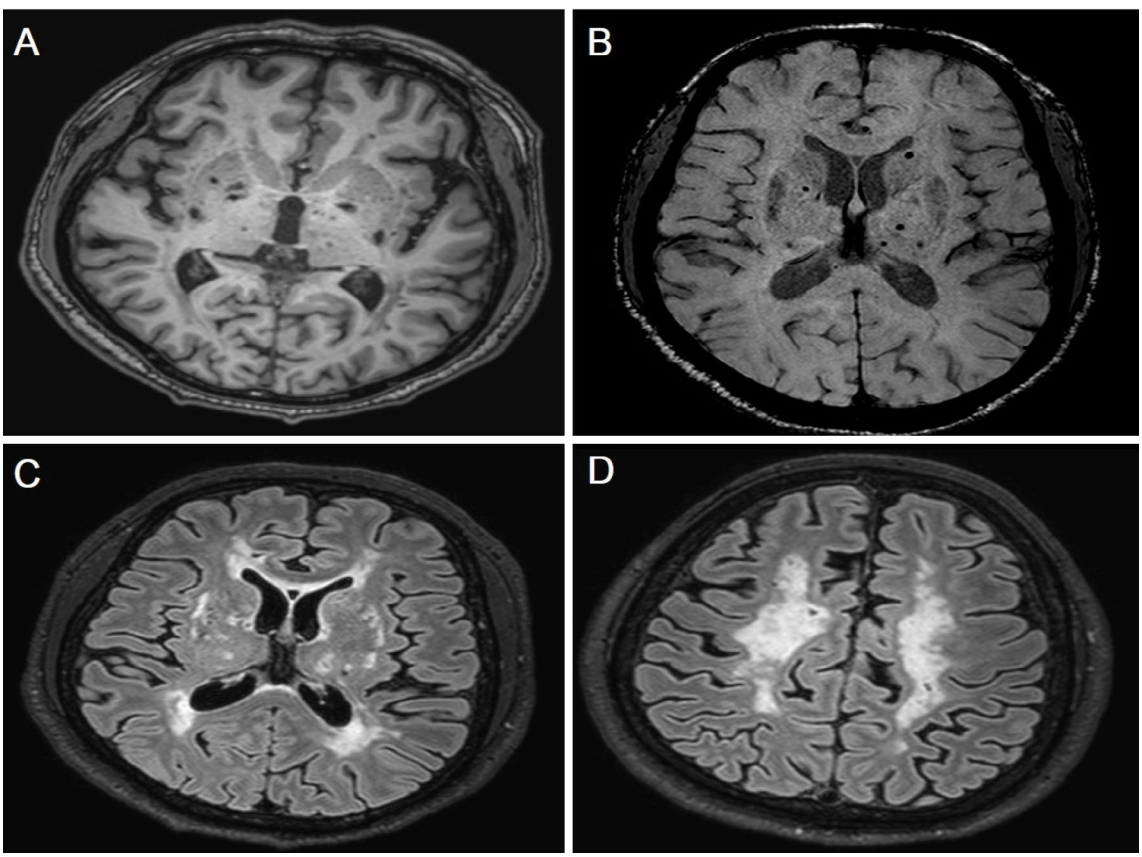

Figure 1. MRI from a 64-year-old patient with CADASIL. (A) 3D T1-weighted image shows lacunes in both basal ganglia. (B) Susceptibility-weighted image shows numerous cerebral microbleeds in both thalami, left the caudate nucleus and right internal capsule. (C-D) Fluid-attenuated inversion recovery image shows periventricular and deep white matter hyperintensities and subcortical lacunes.

Table 2. Univariate logistic analysis of the effects of MRI markers on the dysfunction of each cognitive domain

Domain	MRI markers	OR	95% CI	*p*
Attention	CMBs	1		
	CMBs (1∼2)	2.00	0.35∼11.58	0.439
	CMBs (≥3)	7.33	1.91∼28.10	0.004
	Lacunes	1		
	Lacunes (1∼2)	4.39	0.41∼46.93	0.22
	Lacunes (≥3)	19.83	2.45∼160.39	0.005
	Scheltens score	1.04	1.01∼1.08	0.024
	Hypertension	2.89	1.06∼7.91	0.038
	Diabetes Mellitus	0.61	0.15∼2.47	0.492
Executive Function	CMBs	1		
	CMBs (1∼2)	1.43	0.35∼5.79	0.617
	CMBs (≥3)	6.13	2.07∼18.18	0.001
	Lacunes	1		
	Lacunes (1∼2)	2.4	0.54∼10.67	0.250
	Lacunes (≥3)	9.43	2.67∼33.29	<0.001
	Scheltens score	1.09	1.04∼1.14	<0.001
	Hypertension	3.16	1.27∼7.86	0.0013
	Diabetes Mellitus	2.06	0.57∼7.43	0.272
Memory	CMBs	1		
	CMBs (1∼2)	7.33	1.48∼36.34	0.015
	CMBs (≥3)	10.59	2.75∼40.77	0.001
	Lacunes	1		
	Lacunes (1∼2)	1.36	0.32∼5.89	0.678
	Lacunes (≥3)	3.71	1.16∼11.90	0.027
	Scheltens score	1.05	1.02∼1.09	0.005

sent (grade 1), mild (grade 2, the total number of CMBs, 1-2), and moderate to severe (grade 3, ≥3 CMBs) according to a grading scale described previously[14] because the number of CMBs was not distributed normally. For the same reason, the grade of the lacunes were also grouped as absent (grade 1), mild (grade 2, total number of lacunes, 1-2), and moderate to severe (grade 3, ≥3 lacunes), When a variable showed $p<0.20$ in univariate analysis, multiple logistic regression was performed to evaluate the impact of CMBs on scores for the different cognitive domains. The odds ratio for cognitive dysfunction was calculated using a logistic regression analysis that included age, sex, educational level, hypertension, diabetes mellitus, grade of CMBs, grade of lacunes, and degree of white matter hyperintensity (WMH) (semi-quantitative Scheltens scores). The results of the multivariable analysis included only those variables with a *p*-value less than 0.05. A two-tailed *p*-value <0.05 was considered statistically significant.

RESULTS

Details of the demographics and MRI findings of the subjects with CADASIL are presented in Table 1. The diagnosis was confirmed by NOTCH3 mutation (n=75), and by the skin, a biopsy is showing the presence of granular osmiophilic material (n=8). The sites of mutation were R544C (n=70), R578C (n=2), R75P (n=2), and C452A (n=1). Sixty-nine subjects were symptomatic, and 14 were asymptomatic. Cerebral infarction was the most frequent manifestation (n=32, Fig. 1), followed by chronic headache (n=14), cognitive dysfunction (n=8), ICH (n=8), TIA (n=5), and seizure (n=2). All subjects except one had white matter hyperintensity lesions on the FLAIR images. One or more CMBs on SWI were observed in 58 subjects (69.9%), and one or more lacunes were seen in 63 (75.9%) (Fig. 1).

The results of the univariate analysis to evaluate the impact of MRI markers on each cognitive domain are shown in Table 2. All the MRI markers (grade of CMBs, grade of lacunes, and Scheltens scores) were associated with the attention, executive functioning, and memory domains.

In contrast, only the Scheltens scores showed a significant correlation with the language domain. Hypertension was observed in association with the attention and executive functioning, but these associations disappeared in the

Table 3. Multivariate analyses of the effects of MRI markers on the dysfunction of each cognitive domains

MRI markers	Domain	OR	*p*	95% CI	
				Lower	Upper
CMBs (0)	memory		0.003**		
CMBs (1∼2)	memory	7.33	0.015*	1.48	36.24
CMBs (≥3)	memory	10.59	0.001**	2.75	40.77
Lacunes (0)	attention		0.004**		
Lacunes (1∼2)	attention	4.39	0.846	0.41	46.93
Lacunes (≥3)	attention	19.83	0.005**	2.45	160.39
Lacunes (0)	executive function		0.005**		
Lacunes (1∼2)	executive function	0.84	0.846	0.14	4.91
Lacunes (≥3)	executive function	6.02	0.013*	1.47	24.68
Scheltens scores	executive function	1.10	0.001**	1.04	1.16

Adjusted for age, sex, and education level. CMBs = cerebral microbleeds.
OR = odds ratio; CI = confidence interval. *$p<0.05$, **$p<0.01$, ***$p<0.001$

final multivariate model. In the final multivariate logistic regression model (Table 3), the grade of CMBs was independently associated with the memory domain ($p=0.003$). The moderate to the severe grade of lacunes related to poor performance in the executive domain ($p=0.013$) and attention domain ($p=0.005$). Scheltens scores were associated with poor performance in the executive functioning ($p=0.001$).

DISCUSSION

Our main finding is that in addition to lacunes, CMBs were associated with memory dysfunction in CADASIL. We also found that WMHs were an independent predictor of executive dysfunction. To our knowledge, this is the first study to detect CMBs using SWI, which is associated with much higher rates of CMB detection compared with conventional gradient-echo (GRE).

The frequency of CMBs was very common in patients with CADASIL. It ranges from 25 to 69% in the literature.[11,15-17] However, studies on the relationship between CMBs and cognition are very limited in CADASIL patients. One longitudinal study of CADASIL showed an association between a number of CMBs and memory domain,[12] whereas other studies did not.[18-20] Our results are consistent with the previous longitudinal study showing an association between the number of CMBs and cognitive function, including memory.[12] This longitudinal study, however, recruited a small number of patients (n=25) and did not draw a definite conclusion.[20]

Our new data conflict with our previous data which did not show an association between CMBs and memory dysfunction.This discrepancy may be explained in part by the number of patients enrollment (n=83, new data; n=40, previous data) and different methods of assessment. We used more advanced MRI techniques to detect CMBs compared to our previous studies, including (i) the effects of sequences (traditional GRE versus SWI); (ii) section thickness (5 mm versus 2 mm); and (iii) field strength (1.5 T versus 3 T). Additionally, the present study used CERAD-K, whereas the previous studies used ADAS-cog K. Unlike, in ADAS-cog K, the scores could be z-score transformed in CERAD-K.

Our data cannot rule out the possibility that the number of CMBs might not correlate with memory dysfunction in the early stages of CADASIL. However, it should be noted that memory dysfunction is one of the common problems in CADASIL.[21,22] Seo et al. reported that the number of CMBs was an independent predictor of multiple cognitive domains, including memory, in patients with sporadic subcortical ischemic vascular dementia (SVaD).[23] Moreover, CADASIL and SVaD showed a similar pattern of cognitive deficit in a British CADASIL study.[24] Thus, these results support our hypothesis that the degree of CMBs correlates with memory dysfunction.

We also found strong associations of Scheltens scores with the executive functioning domain. It is generally thought that WMHs are associated with cognitive dysfunction.[25] Although Benisty et al. reported CADASIL patients with isolated WMHs present with executive and attention deficits,[26] the independent effects of WMH volume on cognition in CADASIL patients had not been described before.[27] Our results also demonstrated that three or more lacunes were an independent predictor of executive and attention domains. In our study, CADASIL patients with 2 or fewer lacunes did not show any cognitive dysfunction. We cannot exclude the possibility that one or

two lacunes contributed to cognitive dysfunction in CADASIL. However, our results suggest that the impact of one or two lacunes on cognition is less significant than that of 3 or more lacunes. However, there are limitations in interpreting why there are other impacts on cognitive domains, depending on whether they are CMBs or lacunes. Analysis of the location of CMBs and lacunes has not been done in this study; it is difficult to make conclusions about the effect of CMBs on cognitive domains.

However, this study was a cross-sectional study. Thus, further prospective studies are needed to elucidate the association between CMBs and cognitive dysfunction. Another limitation of our study was that we were not able to investigate whether the location of CMBs is associated with cognition. However, recent studies of the relationship between the location of CMBs and cognition have produced conflicting results.[28] A final limitation was that the severely disabled patients with CADASIL might have been excluded from our study.

We found that grade of CMBs is associated with memory dysfunction and that WMHs may contribute to the prediction of executive dysfunction, therefore, propose that CMBs and WMHs may be useful imaging markers to associated with cognitive dysfunction in CADASIL.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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