

Original Paper

# Cerebral Microbleeds Are Associated with Worse Cognitive Function in the Nondemented Elderly with Small Vessel Disease

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## Key Words

Cerebral microbleeds · Small vessel disease · Cognition

## Abstract

**Background:** Cerebral small vessel disease (SVD) is a leading cause of cognitive decline in the elderly. Cerebral microbleeds (CMBs) have emerged as an important manifestation of cerebral SVD, in addition to lacunar infarcts and white matter lesions (WMLs). We investigated whether the presence and location of CMBs in elderly subjects were associated with cognitive function, independent of lacunar infarcts and WMLs. **Methods:** One hundred and forty-eight nondemented elderly with SVD, defined as the presence of lacunar infarcts and/or WMLs on magnetic resonance imaging (MRI), were studied. Executive function and global cognition were assessed by the Frontal Assessment Battery (FAB) and Mini-Mental State Examination (MMSE), respectively. The differences in the scores for the FAB and MMSE between CMB-positive and CMB-negative subjects were calculated after adjusting for possible confounders. **Results:** The mean age of the subjects was  $72.4 \pm 8.6$  years. CMBs were detected in 48 subjects (32%), with a mean number of CMBs per subject of 1.6 (range 0–31). Among CMB-positive subjects, 42 (87.5%) had CMBs in deep or infratentorial regions with or without lobar CMBs, and 6 (12.5%) had CMBs in strictly lobar regions. The presence of CMBs was significantly associated with FAB and MMSE scores after adjustment for age, years of education, brain volume and the presence of lacunar infarcts (for the FAB) or severe WMLs (for the MMSE). The presence of CMBs in the basal ganglia, in the thalamus or in the lobar regions was associated with FAB scores, while that in the lobar regions was associated with MMSE scores. However, there was no association between CMBs in the infratentorial regions and cognitive

parameters. **Conclusions:** In nondemented elderly with SVD on MRI, the presence of CMBs was independently associated with worse executive and global cognitive functions. CMBs seemed to reflect hypertensive microangiopathy in this population, and CMBs in specific areas may play an important role in cognitive function.

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## Introduction

Cerebral small vessel disease (SVD) is a leading cause of cognitive decline in the elderly [1]. Neuroimaging features of SVD, including lacunar infarcts and white matter lesions (WMLs), are frequently found by brain magnetic resonance imaging (MRI) of elderly people, and are associated with cognitive dysfunction [2–4].

Recently, cerebral microbleeds (CMBs) have emerged as an important new manifestation of SVD that can be detected by gradient-echo T2\*-weighted MRI [5]. Histopathological examinations showed that CMBs are focal hemosiderin depositions in the perivascular space [6, 7]. CMBs in deep or infratentorial regions may reflect hypertensive or atherosclerotic microangiopathy, while CMBs in lobar regions may reflect cerebral amyloid angiopathy (CAA) [8–11]. There has been increasing evidence suggesting an association between CMBs and cognitive function [12]. For example, the presence of CMBs has been reported to be associated with cognitive impairment in healthy adults [13, 14], general elderly populations [15, 16], elderly with increased vascular risk [17] and stroke patients [18–21]. Because CMBs are frequently identified in association with other MRI evidence of SVD, such as WMLs and lacunar infarcts [22], CMBs could be an important cause of cognitive decline in elderly subjects with SVD. However, few studies have so far examined the effect of CMBs on cognition in such a population.

In the present study, we examined nondemented elderly with SVD, defined as the presence of lacunar infarcts and/or WMLs on MRI, and investigated whether the presence and location of CMBs were independently associated with cognitive function.

## Methods

### Patients

A total of 148 nondemented elderly with SVD were examined in the present study. The subjects were enrolled from the outpatients who underwent brain MRI in the Department of Neurology, Juntendo University Shizuoka Hospital, from December 2010 to February 2012. Brain MRI was performed for the assessment of cerebrovascular diseases on the outpatients with  $\geq 1$  vascular risk factors, or with a history of stroke or transient ischemic attack, or with symptoms suspected to be due to cerebrovascular diseases such as dizziness, dysarthria, numbness or weakness of limbs or gait disturbance. The inclusion criteria were the presence of SVD, such as lacunar infarcts and/or WMLs defined as at least Fazekas grade 1 on MRI [23]. The exclusion criteria were territorial infarcts, cerebral hemorrhage, dementia including Alzheimer's disease and vascular dementia, recent/current use of acetylcholine esterase inhibitors, neurodegenerative diseases, psychiatric disease or white matter disease other than ischemia. Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, ed. 4 [24]. Patients with a disability that affected cognitive assessment and those with a disability within 6 months after symptomatic stroke were also excluded.

All study participants provided informed consent, and the study design was approved by the Institutional Review Board of the hospital.

### *Risk Factors*

Cardiovascular risk factors were examined during the study visit by interviews and laboratory examinations. Hypertension was defined as having a systolic blood pressure  $\geq 140$  mm Hg and/or a diastolic blood pressure  $\geq 90$  mm Hg and/or taking antihypertensive medication. Diabetes mellitus was defined as having a fasting blood glucose level  $\geq 126$  mg/dl and/or a HbA1c level  $\geq 6.5\%$  and/or using insulin or oral hypoglycemic agents. Dyslipidemia was defined as having a total cholesterol level  $\geq 220$  mg/dl and/or a triglyceride level  $\geq 150$  mg/dl and/or using lipid-lowering medication. The subjects were considered to be current smokers if they had smoked at least 1 cigarette a day within the previous year. The length of education and history of symptomatic stroke were assessed by self-reports.

### *Brain MRI*

Brain MRI was performed using a 1.5-tesla MR system (Siemens, Magnetom Avanto), and the whole brain was scanned at a slice thickness of 6 mm and an interslice gap of 0.6 mm, obtaining 19 axial images. The imaging protocol consisted of axial T2\*-weighted gradient echo [repetition time (TR)/echo time (TE) = 685/25 ms, flip angle = 20°, field of view (FOV) = 207 × 230, matrix = 218 × 256], axial T1-weighted spin echo (TR/TE = 500/13 ms, FOV = 207 × 230, matrix = 205 × 256), axial T2-weighted fast spin echo (TR/TE = 3,800/91 ms, FOV = 207 × 230, matrix = 288 × 384) and axial fluid-attenuated inversion recovery imaging (FLAIR; TR/TE = 8,500/79 ms, inversion time = 2,500 ms, FOV = 207 × 230, matrix = 230 × 256).

CMBs were defined as small, homogeneous, round foci of low signal intensities on T2\*-weighted images that were  $< 10$  mm in diameter. Basal ganglia calcification and vascular flow voids were excluded. The Microbleed Anatomical Rating Scale (MARS) [25] was used to guide the identification and to describe the location of CMBs. A lacunar infarct was defined as a small lesion (3–15 mm in diameter) with a high signal intensity on T2-weighted images and a low signal intensity on T1-weighted and FLAIR images. Deep and periventricular WMLs were graded from 0 to 3 according to the Fazekas scale [23]. Periventricular hyperintensity or deep white matter hyperintensity of grade  $\geq 2$  was defined as a severe WML [14]. The brain volume (%brain) as an index of brain atrophy was calculated by using the methods described by Koga et al. [26]. Briefly, the area of the cerebral parenchyma on T2-weighted images at two slices above the level of the pineal body was quantitatively measured using a computer-assisted processing system (Image J version 1.48; National Institutes of Health) and was divided by the area inside the skull at the same level to correct for individual differences in head size. The images were analyzed by a trained observer blinded to the patients' clinical data.

### *Cognitive Function*

The cognitive assessment was administered within 2 months of the MRI. Executive function was tested using the Frontal Assessment Battery (FAB) [27]. The FAB is a bedside cognitive and behavioral battery used to assess executive function which consists of 6 subsets: similarities (conceptualization), lexical fluency (mental flexibility), motor series (programming), conflicting instructions (sensitivity to interference), go/no go (inhibitory control) and prehension behavior (environmental autonomy). Global cognition was also tested using the Mini-Mental State Examination (MMSE) [28].

### *Statistical Analysis*

The statistical analyses were performed with the JMP version 9.0 software program (SAS Inc., Cary, N.C., USA). A value of  $p < 0.05$  was considered to be statistically significant. To analyze the associations between the cognitive battery scores and participants' character-

**Table 1.** The characteristics of the study subjects (n = 148)

Age, years	72.4 ± 8.6
Male	79 (53)
Education, years	11.1 ± 2.2
Hypertension	113 (76)
Diabetes mellitus	23 (16)
Dyslipidemia	61 (41)
Current smoker	35 (24)
History of stroke	25 (17)
MRI findings	
Presence of CMBs	48 (32)
Number of CMBs	1.6 ± 4.1
Presence of lacunar infarcts	52 (35)
Presence of severe WMLs	89 (60)
%Brain	80.5 ± 5.6

The data are presented as n (%) of subjects or mean ± SD.

istics, we used the Pearson correlation coefficient for continuous variables and the two-sample t test for categorical variables. The scores for the total and subtests of the FAB and MMSE were compared between CMB-negative and CMB-positive subjects adjusted for age, sex and covariates that were significantly associated with the cognitive battery scores. The relationship between the number of CMBs and the cognitive battery scores was also investigated using a multiple linear regression analysis adjusted for the same covariates.

## Results

The characteristics of the subjects are shown in table 1. The mean age of the study participants was 72.4 ± 8.6 years, and 53% were male. A total of 238 CMBs were found in 48 subjects (32%), with a mean number of CMBs per subject of 1.6 (range 0–31). Of these, 18 subjects (37.5%) had 1 CMB, 12 (25%) had 2–4 CMBs, 12 (25%) had 5–9 CMBs, and 6 (12.5%) had ≥10 CMBs. Among the CMB-positive subjects, 42 (87.5%) had CMBs in deep or infratentorial regions with or without lobar CMBs, and 6 (12.5%) had CMBs in strictly lobar regions. Thirteen subjects (31.0%) had CMBs in both deep and lobar regions. Twenty-five subjects (59.5%) had CMBs in the basal ganglia, 25 (59.5%) had CMBs in the thalamus, 20 (47.6%) had CMBs in the infratentorial regions, and 19 (45.2%) had CMBs in lobar regions (10 in the frontal lobe, 2 in the parietal lobe, 8 in the temporal lobe and 9 in the occipital lobe). The mean age was significantly lower in subjects with CMBs than in those without (70.0 ± 8.0 vs. 73.5 ± 8.6 years,  $p < 0.05$ ). The prevalence of hypertension was significantly higher in subjects with CMBs than in those without (89.6 vs 70.0%,  $p < 0.01$ ), while the rates of other vascular risk factors, such as diabetes mellitus, dyslipidemia and current smoking, were not significantly different between the groups.

The mean FAB total score was 14.7 ± 2.6 (range 8–18), and the mean MMSE total score was 27.6 ± 2.3 (range 22–30). The associations between the cognitive battery scores and subject characteristics are shown in table 2. The FAB total score was significantly correlated with age ( $r = -0.3359$ ), years of education ( $r = 0.3676$ ) and %brain ( $r = 0.3858$ ) and was significantly different between subjects with and without CMBs as well as between those with and without lacunar infarcts. The MMSE total score was significantly correlated with the subjects' age ( $r = -0.1803$ ), years of education ( $r = 0.2437$ ), number of CMBs ( $r = -0.2081$ )

**Table 2.** The associations of FAB and MMSE total scores with the subject characteristics

	FAB	MMSE
Age	-0.3359**	-0.1803*
Sex (male/female)	14.1±2.0/15.0±2.3*	27.3±2.4/27.8±2.2
Education	0.3676**	0.2437**
Hypertension (yes/no)	14.1±2.0/15.0±2.3*	27.3±2.4/27.8±2.2
Diabetes mellitus (yes/no)	14.1±2.0/15.0±2.3*	27.3±2.4/27.8±2.2
Dyslipidemia (yes/no)	14.1±2.0/15.0±2.3*	27.3±2.4/27.8±2.2
Current smoker (yes/no)	14.1±2.0/15.0±2.3*	27.3±2.4/27.8±2.2
History of symptomatic stroke (yes/no)	14.1±2.0/15.0±2.3*	27.3±2.4/27.8±2.2
MRI findings		
CMBs (yes/no)	13.9±2.4/15.0±2.1**	26.8±2.6/28.0±2.0**
Number of CMBs	-0.1528	-0.2143*
Lacunar infarcts (yes/no)	14.1±2.0/15.0±2.3*	27.3±2.4/27.8±2.2
Severe WMLs (yes/no)	14.4±2.43/15.1±2.1	27.3±2.4/28.1±1.9*
%Brain	0.3858**	0.2844**

\* p < 0.05; \*\* p < 0.01.

**Table 3.** The results of a comparison of the cognitive parameters between CMB-positive and CMB-negative subjects

	CMB-positive (n = 48)	CMB-negative (n = 100)	p <sup>1</sup>
FAB			
Total score (/18)	13.9±2.4	15.0±2.1	0.007
Similarities (/3)	2.2±0.5	2.4±0.6	0.02
Lexical fluency (/3)	1.8±0.7	2.0±0.8	0.57
Motor series (/3)	2.1±1.2	2.5±0.9	0.07
Conflicting instructions (/3)	2.8±0.5	2.8±0.5	0.55
Go/no go (/3)	2.0±0.9	2.3±0.8	0.04
Prehension behavior (/3)	3.0±0.0	3.0±0.0	–
MMSE			
Total score (/30)	26.8±2.6	28.0±2.0	0.009
Orientation (/10)	9.4±1.1	9.8±0.7	0.19
Registration (/3)	3.0±0.0	3.0±0.0	–
Attention and calculation (/5)	3.2±1.7	3.7±1.6	0.02
Recall (/3)	2.3±0.9	2.5±0.7	0.95
Language (/2)	2.0±0.0	2.0±0.0	–
Repetition (/1)	0.9±0.3	1.0±0.1	0.01
Complex commands (/6)	5.9±0.2	6.0±0.2	0.12

<sup>1</sup> Adjusted for age, sex, years of education, %brain and the presence of lacunar infarcts (for the FAB) or severe WMLs (for the MMSE).

and %brain (r = 0.2844) and was significantly different between subjects with and without CMBs as well as between those with and without severe WMLs.

Table 3 shows a comparison of the cognitive parameters between CMB-negative and CMB-positive subjects. The CMB-positive subjects had significantly lower scores on the FAB (total score, similarities, go/no go) and the MMSE (total score, attention and calculation, repe-

**Table 4.** The relationship between locations of CMBs and cognitive parameters

	Basal ganglia		Thalamus		Lobar	
	positive (n = 25)	negative (n = 123)	positive (n = 25)	negative (n = 123)	positive (n = 19)	negative (n = 129)
<b>FAB</b>						
Total score (/18)	13.6±2.4	14.9±2.2*	13.6±2.6	14.9±2.1*	13.4±2.4	14.9±2.2*
Similarities (/3)	2.2±0.5	2.4±0.6	2.1±0.5	2.4±0.6	2.2±0.5	2.4±0.6
Lexical fluency (/3)	1.6±0.7	2.0±0.8	1.7±0.7	2.0±0.8	1.7±0.7	2.0±0.8
Motor series (/3)	2.0±1.3	2.5±0.9	2.1±1.2	2.5±0.9	2.0±1.2	2.5±0.9
Conflicting instructions (/3)	2.7±0.6	2.8±0.5	2.6±0.6	2.8±0.5	2.7±0.6	2.8±0.5
Go/no go (/3)	2.0±0.8	2.2±0.8	2.0±0.9	2.2±0.8	1.9±0.9	2.2±0.8
Prehension behavior (/3)	3.0±0	3.0±0	3.0±0	3.0±0	3.0±0	3.0±0
<b>MMSE</b>						
Total score (/30)	26.8±2.7	27.7±2.2	26.5±3.0	27.8±2.1	26.2±3.1	27.8±2.1*
Orientation (/10)	9.4±1.0	9.7±0.8	9.2±1.4	9.8±0.6*	9.5±1.2	9.7±0.8
Registration (/3)	3.0±0	3.0±0	3.0±0	3.0±0	3.0±0	3.0±0
Attention and calculation (/5)	3.2±1.6	3.6±1.6	3.2±1.7	3.6±1.6	2.8±1.8	3.7±1.6*
Recall (/3)	2.4±0.9	2.5±0.7	2.2±0.9	2.5±0.7	2.2±0.9	2.5±0.7
Language (/2)	2.0±0	2.0±0	2.0±0	2.0±0	2.0±0	2.0±0
Repetition (/1)	0.9±0.3	1.0±0.2	0.9±0.3	1.0±0.2	0.8±0.4	1.0±0.1**
Complex commands (/6)	6.0±0.2	5.9±0.2	5.9±0.3	6.0±0.2	5.9±0.3	6.0±0.2

\* p < 0.05, \*\* p < 0.01, for comparisons between the CMB-positive and -negative groups; adjusted for age, sex, years of education, %brain and the presence of lacunar infarcts (for the FAB) or severe WMLs (for the MMSE).

tion) than did the CMB-negative subjects after adjustment for age, sex, years of education, %brain and the presence of lacunar infarcts (for the FAB) or severe WMLs (for the MMSE). The number of CMBs was not significantly associated with MMSE scores after adjustment for the same covariates.

The association between the locations of CMBs and cognitive parameters was also analyzed after adjusting for the same covariates (table 4). The presence of CMBs in the basal ganglia, in the thalamus or in the lobar regions was associated with a significant reduction in FAB total score. Subjects with lobar CMBs had significantly lower scores on the MMSE (total, attention and calculation, repetition) than those without. In addition, the subjects with thalamic CMBs had significantly lower scores on the ‘orientation’ subtests of the MMSE. There was no association between the presence of CMBs in infratentorial regions and cognitive parameters.

## Discussion

Our study showed that the presence of CMBs was significantly associated with both executive function and global cognition in nondemented elderly individuals with SVD, which was defined as the presence of lacunar infarcts and/or WMLs on MRI. This association was independent of coexisting lacunar infarcts, WMLs and other possible confounders.

An association between CMBs and global cognitive dysfunction, as assessed by the MMSE or Montreal Cognitive Assessment (MoCA), has been reported in the healthy adults [14, 15], a general elderly population [16] and stroke patients [21]. We used the MMSE to assess cognition, because this scale is a widely used instrument of cognitive assessment for patients

with SVD. However, it has been suggested that the MMSE has a relatively low sensitivity for the assessment of cognitive function in these patients [28]. Executive dysfunction is a characteristic feature of SVD [29], and CMBs have been reported to be associated with executive function in the general elderly populations [15, 16] and stroke patients [18–20]. In our study, we used the FAB to assess executive function. The FAB score has been reported to be associated with the severity of WMLs in atherosclerotic high-risk patients without dementia [30]. Our study showed that executive function and global cognition, as assessed by the FAB and MMSE, were significantly associated with the presence of CMBs in nondemented elderly individuals with SVD. The RUN DMC Study has also examined nondemented elderly individuals with SVD on MRI [31]. The study group showed that the presence of CMBs was associated with impairment of global cognition and executive function, such as psychomotor speed and attention, which is consistent with the results of our study.

In our study, when the presence of CMBs was divided into specific locations, executive function was found to be associated with CMBs in the basal ganglia as well as in the thalamus and in the lobar regions, while global cognition was associated with CMBs in the lobar regions. However, there was no association between CMBs in the infratentorial regions and the cognitive parameters. These findings suggest that CMBs in specific areas could play a significant role in cognitive function. The frontal lobe, the basal ganglia and the thalamus participate in the frontal-subcortical circuits involved in executive function [32]. The presence of CMBs in these regions has been reported to be associated with cognitive impairment in a general elderly population [14], stroke patients [18–21] and nondemented elderly individuals with SVD in the RUN DMC Study [31]. It has been suggested that CMBs may cause direct structural damage to the surrounding brain tissue, leading to the disconnection of functionally important cortical and subcortical structures [18]. In addition, the presence of CMBs may reflect more diffuse brain damage. A recent study using diffusion tensor imaging has shown that the presence of CMBs was associated with a poorer global microstructural integrity of the brain white matter, even when only a single CMB was present [33].

The location of CMBs is related to underlying vascular pathologies, such as hypertensive microangiopathy and CAA [8–11]. In our study, most of the subjects (87.5%) had CMBs in the deep or infratentorial regions, and only a few had CMBs in strictly lobar regions (12.5%). Thus, hypertensive microangiopathy, rather than CAA, might be the most likely underlying etiology of CMBs in our subjects. However, approximately 30% of subjects with deep CMBs also had CMBs in lobar regions. A histopathological study indicated the coexistence of both pathogenic mechanisms in patients having CMBs located in both deep and lobar regions [6]. Another recent study using *in vivo* imaging of amyloid with <sup>11</sup>C-Pittsburgh compound B positron emission tomography in patients with cognitive impairment suggested that both the CAA and subcortical SVD contributed to the pathogenesis of lobar CMBs in patients having CMBs in both deep and lobar regions [34]. However, whether this is also the case in nondemented elderly subjects with SVD, as were our subjects, is currently unknown.

There are some limitations associated with our study. First, it had a cross-sectional design, and prospective studies are needed to establish causality. Second, we included subjects suspected to have SVD based on the presence of lacunar infarcts or WMLs, defined as at least Fazekas grade 1 on MRI. Although our subjects consisted of outpatients with a high prevalence of vascular risk factors, minimal WMLs (Fazekas grade 1) can be associated with non-SVD causes such as aging [35]. Unexpectedly, the mean age of the subjects with CMBs was significantly lower than that of the patients without. On the other hand, the prevalence of hypertension was significantly higher in subjects with CMBs than in those without. These findings might be associated with the recruitment of our subjects, in whom hypertension, rather than age, might have more strongly influenced the presence of CMBs. Third, although we found an association between cognition and lobar CMBs, we cannot rule out the influence

of coexisting neuropathologies due to Alzheimer's disease. Fourth, the number of subjects in the present study was small, particularly when considering the subgroups with different CMB location. Further studies with larger sample sizes are required to confirm our findings. Finally, the FAB and MMSE, used for the assessment of cognitive functions in the present study, are screening tools, and more appropriate neuropsychological tests are needed to permit detailed analyses of the specific domains of cognitive function.

In conclusion, our study suggests that the presence of CMBs is associated with worse executive and global cognitive functions in nondemented elderly subjects with SVD on MRI. CMBs seemed to reflect hypertensive microangiopathy in this population, and those located in specific areas may play an important role in cognitive function.

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### Disclosure Statement

The authors declare no financial or other conflict of interest.

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