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Neuropsychological Features of Microbleeds and Cortical Microinfarct Detected by High Resolution Magnetic Resonance Imaging

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Abstract.
Background: Lobar microbleeds (MBs) and cortical microinfarct (CMI) are caused by cerebral amyloid angiopathy in the elderly and increase in number in Alzheimer's disease.
Objective: The aim of this study is to elucidate the effects of lobar MBs and CMIs on cognitive function.
Methods: The subjects were outpatients who visited the memory clinic of Mie University Hospital. Among 120 subjects, 109 patients fulfilled the inclusion criteria. We quantitatively estimated MBs and CMIs using double inversion recovery and 3D FLAIR images of 3T MRI. Neuropsychological assessments included intellectual, memory, constructional, and frontal lobe function.
Results: Of the 109 patients, MBs and CMIs were observed in 68 (62%) and 17 (16%) subjects, respectively. Of the 68 patients with MBs, lobar MBs were found in 28, deep MBs in 8 and mixed MBs in 31. In each age group, the number of MBs increased in patients with CMI (CMI+ group) than those without CMI (CMI– group), and MBs and CMIs additively decreased MMSE scores. In psychological screens, the MBs+ group with more than 10 MBs showed significantly lower scores of category- and letter-WF than MB- group. The CMI+ group showed significantly worse scores than CMI– group in Japanese Raven's coloured progressive matrices, Trail Making Test-A, category- and letter-word fluency and copy and drawing of figures.
Conclusion: Lobar MBs and CMIs in the elderly frequently coexisted with each other and additively contributed to cognitive impairment, which is mainly predisposed to frontal lobe function.

Keywords: Bleeding, cerebral amyloid angiopathy, dementia, infarct, magnetic resonance imaging, neuropsychological test

INTRODUCTION

The main pathological features of small vessel disease (SVD) contain microbleeds (MBs), lacunar infarctions, white matter lesions (leukoaraiosis), and cortical microinfarcts (CMIs) [1]. These MBs

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are characterized by small (less than 5 or 10 mm in diameter), homogeneous, and round foci of low signal intensity [2] and are distributed in the lobar (cortical and subcortical region) region or alternatively, the deep/infratentorial region including the basal ganglia, thalamus, and infratentorial structures [2]. A close correlation has been shown between deep/infratentorial MBs and hypertensive SVD, and also between lobar MBs and cerebral amyloid angiopathy (CAA) [3].

On the other hand, CMIs are defined as sharply demarcated microscopic regions of cellular death or tissue necrosis [4] and remained invisible in conventional magnetic resonance imaging (MRI) [5]. In pathological specimens, CMIs are distributed predominantly in the parietal and occipital lobes [6, 7] and watershed regions [8]. They are encountered in 16 to 46% of elderly people in any cause of death [4] or 33% in cognitively normal elderly people [9]. CMIs have been attributed to CAA and found frequently in Alzheimer's disease (AD) brains [6, 10]. More Recently, van Rooden et al. have reported that CMIs are found more numerously in AD compared to control subjects, and have been negatively correlated to cognitive function in clinicopathological observations [11]. More recently, van Veluw et al. [12] has reported worse clinical correlates in memory clinic patients with CMI, but it remains uncertain whether difference of detection methods, ethnic populations, and degree of other small vessel disease may affect negative relationship between CMI and cognitive function.

We have reported a novel method for *in vivo* detection of CMIs using 3T MRI [13], and suggested that CMIs and lobar MBs share a common etiology in dementia patients. The detection of CMIs by high resolution MRI has been further reported using 7T MRI [11, 14] and 3 T MRI [15]. The purpose of the present study is to clarify the correlation of lobar MBs, CMIs, and cognitive dysfunction and further, neuropsychological characteristics of patients with these amyloid-related vasculopathy.

MATERIALS AND METHODS

Subjects

We prospectively registered 120 patients who consulted the memory clinic of our hospital and registered for this study with high-resolution 3T MRI and screening with neuropsychological tests. All procedures followed the Clinical Study Guidelines of the Ethics Committee of Mie University Hospital and were approved by the internal review board. A complete description of all procedures was provided to the patients, and written informed consent was obtained from them or their caregivers. Every patient was examined comprehensively by neurologists with sufficient experience in examining patients with dementia. We collected data from the patients who fulfilled the following inclusion criteria: 1) consulted with the Memory Clinic of our hospital from October 2011 to June 2013, 2) had a neuroimaging examination using 3T-MRI, 3) had completed neuropsychological assessments, and 4) had blood laboratory examination. Exclusion criteria were as follows: The patients 1) declined or could not be examined by MRI, 2) declined neuropsychological assessments, 3) were diagnosed with treatable dementia, and 4) had normal cognitive function.

All diagnoses were based on pre-established criteria: For AD, fulfilling the criteria for probable AD of the National Institute of Neurologic Disorders and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) [16]; for vascular dementia (VaD), fulfilling the criteria for probable VaD of the National Institute of Neurologic Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [17]; for mild cognitive impairment (MCI), fulfilling the general criteria of the International Working Group on MCI [18]; for dementia with Lewy bodies (DLB), fulfilling the clinical criteria of the consortium on DLB [19]; for frontotemporal lobar degeneration, fulfilling the Lund-Manchester criteria for behavioral variant frontotemporal dementia, semantic dementia, or progressive nonfluent aphasia [20]; for CAA, represented by Charidimou [1]; and for AD with cerebrovascular disease by Bruandet [21].

Laboratory tests included thyroid-stimulating hormone, free thyroid 3, free thyroid 4, treponema palladium hemagglutination, vitamin B1, vitamin B12, folic acid, thyroglobulin autoantibody, and thyroid peroxidase.

MR imaging protocol

MR imaging protocol was the same protocol of Ii et al. [13]. Briefly, MRI studies were performed with a 3T MR unit (Achieva, Philips Medical System, Best, the Netherlands) using an 8- or 32- channel phased-array head coil. We used double inversion

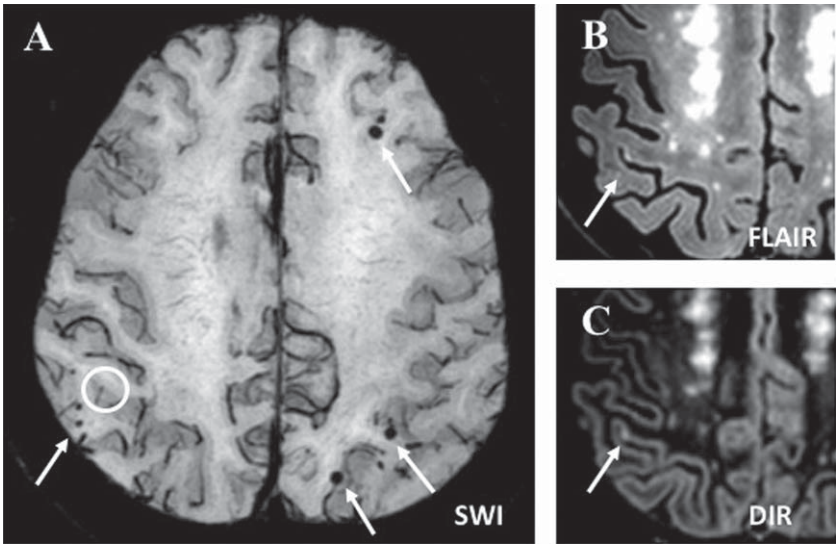

Fig. 1. Representative images of MBs and CMI in a patient with Alzheimer's disease. Arrows in (A) indicate MBs and a circle indicates location of CMI. Arrows in (B, C) indicate CMI.

recovery (DIR) and 3D-fluid attenuated inversion recovery (FLAIR) images, to detect CMI *in vivo*. Axial DIR imaging was performed using two different inversion pulses. The long inversion time and the short inversion time were defined as the intervals between the 180° inversion pulse and the 90° excitation pulse, respectively, which had been optimized for human brain imaging and were provided by the vendor.

Details of the 2D and 3D DIR protocol were as follows: Field of view, 230 mm; matrix, 320 × 256 (512 × 512) after reconstruction; in-plane resolution, 0.45 mm × 0.45 mm); section thickness, 3 mm with no intersection gap; no parallel imaging; repetition time (ms)/echo time (ms), 15,000/28; long inversion time (ms)/short inversion time (ms), 3,400/325; number of signals acquired, two; and acquisition time, 4 min 30 s for 2D, field of view, 250 mm; matrix, 208 × 163 (256 × 256) after reconstruction; in plane resolution, 0.98 mm × 0.98 mm); section thickness, 0.65 mm with over contiguous slice; TSE factor 173; repetition time (ms)/echo time (ms), 5,500/247; long inversion time (ms)/short inversion time (ms), 2,550/450; number of signals acquired, two; and acquisition time, 5 min 13 s for 3D.

The details of susceptibility-weighted imaging (SWI) were follows: Field of view, 230 mm; matrix, 320 × 251 (512 × 512 after reconstruction; in-plane resolution, 0.45 mm × 45 mm); section thickness, 0.5 mm with over contiguous slice; repetition time (ms)/echo time (ms), 22/11.5 (in-phase), 33 (shifted); number of signals acquired, one; flip angle 20° and acquisition time, 5 min 45 s. 3D FLAIR imaging was obtained in a sagittal direction, and then the axial and coronal images were reconstructed. The details of 3D FLAIR were as follows: Field of view, 260 mm; matrix, 288 × 288 (364 × 364 after reconstruction; in-plane resolution, 0.68 × 0.67 mm); section thickness, 1 mm with 0.5 mm overlap; no parallel imaging; repetition time (ms)/echo time (ms), 6,000/400; inversion time, 2,000 ms; number of signals acquired, two; and acquisition time, 5 min 12 s.

Evaluation of CMI and MBs on MR imaging

MBs were defined on SWI images as small (<10 mm), homogeneous, round foci [2] (Fig. 1A), and were assessed by 2 separate raters, who were blinded to diagnosis followed by a consensus reading. CAA was defined on the basis of the location and presence of MBs according to the Boston criteria [22]. MBs were counted throughout the brain and categorized as 'deep' in the basal ganglia/thalamus (including the internal and external capsule), 'infratentorial' (brain stem and cerebellum), and 'lobar' (cerebral cortex and subcortical and periventricular white matter) regions. If the MBs were observed at both lobar and deep regions, the subject was classified as 'mixed MBs'. Lobar MBs were subgrouped as frontal, temporal, parietal, and occipital. When at least one small hypointense focus was

detected, the region or area of the brain was defined as MBs-positive.

CMI was defined as small cortical hyperintense lesions not contiguous to white matter hyperintensities, with a maximum diameter of 5 mm, and a round or elliptical shape, not connected to other structures (tubular shapes, white matter hyperintensities, or white matter tracts) (Fig. 1B, C). CMI was independently assessed on DIR images by two separate raters. Only cortical or juxtacortical lesions with the same or a higher intensity than the relatively hyperintense outer cortex layer were scored. The cortical and juxtacortical location was confirmed in sagittal, coronal, and transverse directions. If the location could not be determined exactly on the DIR images, the location was determined on FLAIR images.

For the detection of CMIs, we utilized both the FLAIR and DIR, based on the reported literatures which investigated the cortical lesion of patients with multiple sclerosis [e.g., 23–26]. The literature showed that the DIR was useful to detect the cortical lesion of multiple sclerosis patients. In the present study, we judged the existence of CMI only when the lesion was detected by both FLAIR and DIR image on an ultrahigh-field MR scanner. That means our criterion is relatively tight.

Neuropsychological assessments

The following tests were performed: For intellectual ability, Mini-Mental State Examination (MMSE) and Japanese Raven's Coloured Progressive Matrices (RCPM) [27]; for memory, Rivermead Behavioral Memory Test (RBMT) [28]; for visuospatial function, the construction test (Copy and Drawing of cube and Necker cube) [29]; for frontal lobe function, Word fluency (WF: Category Cue task, animal; Letter Cue task, ta, te, sa, ka), and Trail making test-A/-B (TMT-A, TMT-B).

Statistical analyses

Statistical analyses were performed with the Statistical Package for the Social Sciences, Version 20 (SPSS, Chicago, Illinois). Group comparisons with respect to the number of CMI and MBs were performed by using independent *t*-tests for continuous data, and chi-square tests for dichotomous data, and Mann-Whitney U tests for nonparametric data. Differences of $p = 0.05$ were considered statistically significant.

RESULTS

Study population

Consequently, 120 patients have been registered for this study and 109 patients fulfilled the inclusion criteria (Fig. 2). The distribution of number of MBs has the border at 10, therefore, we used 10 as a classification standard of MBs (Supplementary Fig. 1). Of the 109 patients, 47 had MBs from 1 to 9, and 21 had 10 or more. All 28 patients with lobar MBs had less than 10 MBs, whereas 21 of 31 (67.7%) patients with mixed MBs had 10 or more MBs (Fig. 2). In the both DIR and 3D FLAIR images, CMIs were observed in 17 patients, and, among them, 9 patients belonged to the group of over 10 MBs and 3 to the group of 1–9 MBs (Fig. 3). There were 5 patients with CMI but without MBs, and this finding was dissociated from our previous research showing that all patients with CMI accompanied MBs [13]. We performed the statistical analyses about the prevalence and association of MBs and CMI by diagnosis (Supplementary Table 1). The results of multiple comparison showed that numbers of MBs of CAA were significantly greater than AD ($p = 0.015$). The result of numbers of CMI showed no significant differences in diagnosis. We analyzed the lobar distribution of MBs and CMIs (Supplementary Table 2a, b). There were significant differences between frontal and parietal on MBs as a result of multiple comparison ($p < 0.001$).

We performed the analysis of comparing between CMIs+/MBs+ and CMIs+/MBs–. There was no significant difference on any neuropsychological assessments (Supplementary Table 3). However, analysis of comparing between CMIs+/MBs– and CMIs–/MBs– showed significant differences on age, RCPM time, and WF (Category) (Supplementary Table 4). Furthermore, we performed the generalized linear model with the negative binomial distribution analysis about the CMI and MBs for the cognition (Supplementary Tables 5 and 6). These results showed that CMI significantly have effect on TMT-A and WF (letter).

MBs

Between the MBs+ and MBs– groups, there were significant difference in the frequency of education ($p = 0.003$) and hyperlipidemia ($p = 0.027$). Neuropsychological assessment showed a decreased score in category- ($p = 0.004$) and letter-WF ($p = 0.004$) and increased score in copy-Construction

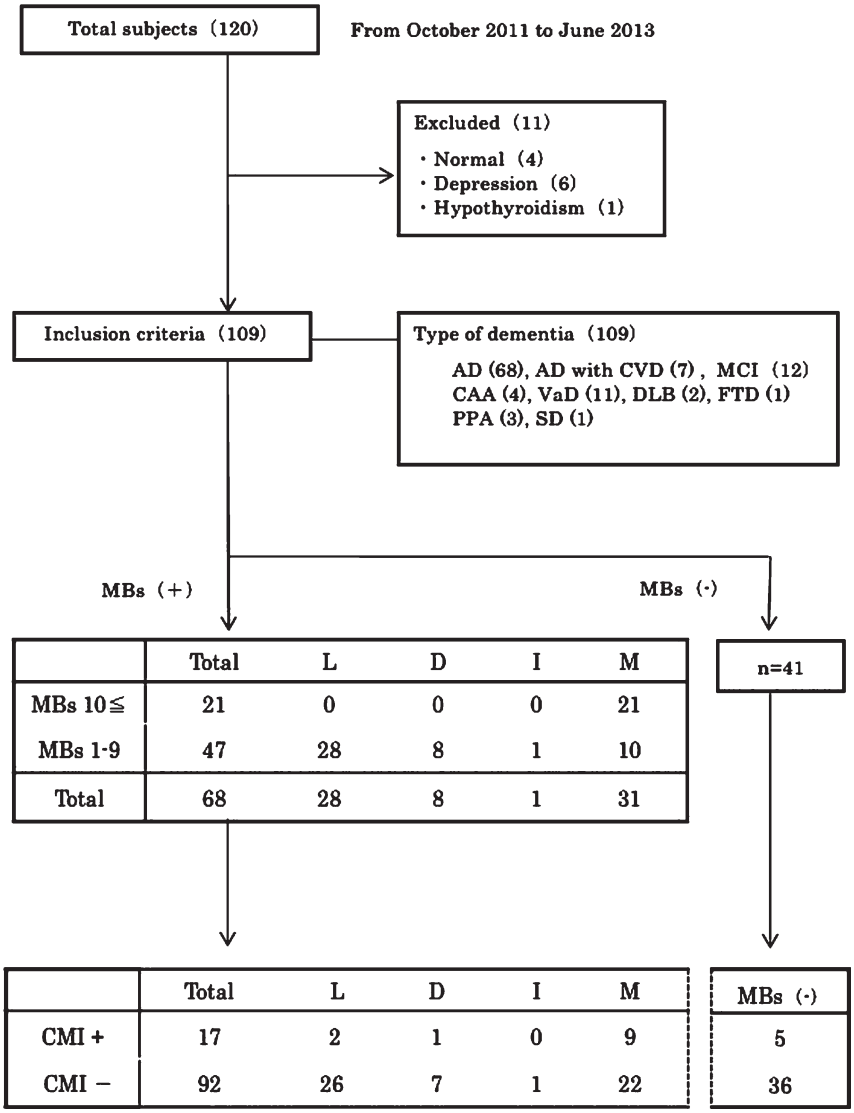

Fig. 2. Flow diagram of inclusion, exclusion and MRI diagnosis of the 109 subjects. The digits in the parentheses show the number of the patients. + and – shows the positive and negative, respectively: AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; CMI, cortical microinfarct; CVD, cerebrovascular disease; D, deep; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; I, infratentorial; L, lobar; M, mixed; MBs, microbleeds; MCI, mild cognitive impairment; PPA, primary progressive aphasia; SD, semantic dementia.

($p = 0.047$) in the MBs+ group (Table 1). According to the number of MBs, there were significant differences exclusively in category- and letter-WF between the MBs– group, the MBs+ group from 1 to 9 and 10 or more. In these groups, the number of words for category were 11.4 ± 3.7, 9.5 ± 4.1, and 8.0 ± 3.4, respectively, whereas those for letter were 5.7 ± 2.0, 4.9 ± 2.0, and 3.9 ± 1.6, respectively. The MBs+ group with more than 10 MBs showed significantly lower scores of category- and letter-WF than MB- group. From the standpoint of MBs location, there were significant differences exclusively in category- and letter-WF between the lobar, deep and mixed MBs groups. The number of words for category were 9.8 ± 4.4, 8.1 ± 4.1, and 8.6 ± 3.4, respectively, whereas those for letter were 4.9 ± 2.1, 4.7 ± 1.3, and 4.4 ± 1.9, respectively. The difference between MBs- and mixed type distribution of MBs was in category-WF ($p = 0.04$). The results of TMT-A/B of our subjects were prolonged compared to normal subjects. The normal range of TMT-A and B are as follows: A; 70–74 year-old 117.3 ± 30.8, 75–79 y.o. 123.1 ± 30.5, B; 70–74 y.o. 167.2 ± 46.9, and 75–79 y.o. 179.5 ± 48.4. Both the MBs- (TMT-A

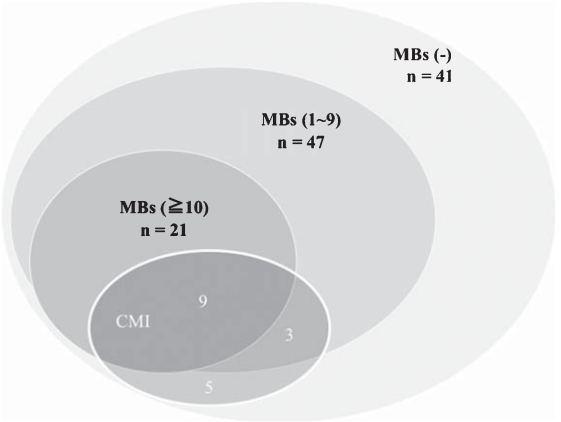

Fig. 3. Distribution of MBs and CMI in the 109 patients.

197 ± 89, -B 301 ± 142) and MBs+ groups (TMT-A 233 ± 132, -B 280 ± 130) were impaired. We may say that, because the TMT is more difficult than WF, the discrepancy between them appeared.

CMI

Of the 17 with CMI, there were 9 patients with mixed MBs, 2 with lobar MBs, and 1 with deep MBs. Between the CMI+ and CMI– groups, there was significant difference in age ($p < 0.001$). Neuropsychological assessment showed significantly worse scores in RCPM ($p = 0.025$), TMT-A ($p = 0.023$), category- ($p = 0.05$) and letter-WF ($p = 0.006$), and drawing of figures ($p = 0.034$) (Table 2). The average number of MBs was 51.7 ± 137.2 in the CMI+ group and 6.0 ± 16.1 in the CMI- group, being more numerously in the CMI+ group ($p = 0.027$). With advancing ages, there were trends for numerical increase of MBs only when CMIs coexisted (Fig. 4A). About the relationship between MMSE scores, MBs, and CMIs, the MMSE score was significantly lower in the CMI+ group than the CMI- group ($p = 0.01$) exclusively in the MBs+ group (10 or more) (Fig. 4B). Among the subjects with mixed MBs distribution, the CMI+ group showed significantly worse scores of MMSE ($p = 0.002$), TMT-A ($p = 0.008$), and category- and letter-WF ($p = 0.004$; $p < 0.001$) (Table 3).

Stroke, white matter lesions, atrophy

There were three patients with cerebral infarct in the present study. The results of neuropsychological assessments between presence and absence of cerebral infarct did not show any significant differences (Supplementary Table 7). Regarding lacunar infarction, patients with lacunar infarction were significant worse than those patients without in the RCPM score, RBMT (SPS, SS), TMT-A, and WF (category) (Supplementary Table 8). Assessment of white matter lesion using Fazekas scale (PVH) showed that value of scale was more severe; value of MMSE, RCPM-score, TMT-A, and WF (category and letter) were worse (Supplementary Table 9). Assessment of white

Table 1
Characteristics and neuropsychological assessments of the patients with or without MBs

		MBs (+) *n*=68	MBs (–) *n*=41	*p*-value
Demographics				
Age		76.4 (6.5)	74.0 (7.3)	0.083
Male		26 (38.2%)	16 (39.0%)	0.16
Education (years)		10.2 (3.1)	11.8 (2.2)	0.003*
Hypertension		43%	37%	0.53
Hyperlipidemia		9%	24%	0.027*
Diabetes mellitus		10%	12%	0.76
Neuropsychological assessments				
MMSE		22.3 (4.2)	22.9 (4.4)	0.49
RCPM	Score	24.8 (5.8)	25.2 (5.8)	0.76
	Time (s)	528 (263)	503 (279)	0.48
RBMT	SPS	7.2 (5.8)	6.9 (6.2)	0.64
	SS	2.6 (2.6)	2.5 (2.9)	0.71
TMT	A (s)	233 (132)	197 (89)	0.24
	B (s)	280 (130)	301 (142)	0.55
WF	Category	9.0 (3.9)	11.4 (3.7)	0.004*
	Letter	4.6 (1.9)	5.7 (2.1)	0.004*
Construction	Copy	2.6 (0.6)	2.8 (0.7)	0.047*
	Drawing	2.2 (1.0)	2.4 (0.8)	0.19

MBs, Microbleeds; MMSE, Mini-Mental State Examination; RBMT, Rivermead Behavior Memory Test; RCPM, Raven's Colored Progressive Matrices; TMT, Trail-Making Test; WF, word fluency.

Table 2
Characteristics and neuropsychological assessments of the patients with or without CMI

		CMI (+) n=17	CMI (–) n=91	p-value
Demographics				
Age		80.0 (2.6)	74.7 (7.2)	<0.001*
Male		9 (52.9%)	33 (35.9%)	<0.001*
Education (years)		11.0 (3.3)	10.7 (2.8)	0.97
Hypertension		41%	41%	0.97
Hyperlipidemia		18%	14%	0.72
Diabetes mellitus		18%	10%	0.35
Neuropsychological assessments				
MMSE		20.9 (4.2)	22.8 (4.3)	0.087
RCPM	Score	22.1 (6.2)	25.5 (5.6)	0.025*
	Time (s)	540 (202)	513 (281)	0.3
RBMT	SPS	6.5 (5.2)	7.2 (6.1)	0.84
	SS	2.0 (2.1)	2.6 (2.8)	0.62
TMT	A (s)	289 (141)	204 (105)	0.023*
	B (s)	235 (118)	293 (136)	0.43
WF	Category (/min)	8.2 (4.7)	10.3 (3.7)	0.05*
	Letter (/min)	3.8 (2.0)	5.3 (1.9)	0.006*
Construction	Copy	2.6 (0.5)	2.7 (0.7)	0.11
	Drawing	1.8 (1.0)	2.3 (0.9)	0.034*

CMI, cortical microinfarct; MMSE, Mini-Mental State Examination; RBMT, Rivermead Behavior Memory Test; RCPM, Raven's Colored Progressive Matrices; TMT, Trail-Making Test; WF, word fluency.

Table 3
Comparison of neuropsychological assessments between patients with or without CMIs among those with mixed MBs

		CMI (+), n=9	CMI (–), n=21	p-value
Demographics				
Age		78.7 (2.9)	77.2 (4.5)	0.42
Male		3 (33.3%)	9 (42.9%)	0.15
Education (years)		9.3 (2.0)	10.4 (3.1)	0.41
Hypertension		44%	48%	0.9
Hyperlipidemia		0%	10%	0.69
Diabetes mellitus		11%	5%	0.79
Neuropsychological assessments				
MMSE		18.6 (3.1)	23.4 (3.7)	0.002*
RCPM	Score	21.6 (4.8)	25.0 (5.9)	0.24
	Time (s)	552 (216)	584 (326)	0.89
RBMT	SPS	4.4 (3.3)	8.4 (6.2)	0.14
	SS	1.0 (0.9)	3.2 (2.9)	0.09
TMT	A (s)	324 (144)	184 (86)	0.008*
	B (s)	407	250 (107)	0.46
WF	Category (/min)	6.1 (2.6)	9.9 (3.1)	0.004*
	Letter (/min)	2.8 (1.3)	5.2 (1.5)	<0.001*
Construction	Copy	2.4 (0.5)	2.8 (0.4)	0.18
	Drawing	1.4 (1.0)	2.2 (0.8)	0.056

MBs, Microbleeds; CMI, cortical microinfarct; MMSE, Mini-Mental State Examination; RBMT, Rivermead Behavior Memory Test; RCPM, Raven's Colored Progressive Matrices; TMT, Trail-Making Test; WF, word fluency.

matter lesion using Fazekas scale (DWMH) showed that value of scale was more severe; value of RCPM-time, RBMT (SPS, SS), and TMT-A were worse (Supplementary Table 10). Regarding atrophy, Evans index showed that there was no significant difference between right and wrong score (Supplementary Table 11).

DISCUSSION

The findings of the present study were summarized as follows: i) among 109 subjects who fulfilled the inclusion criteria, MBs and CMIs were observed in 68 and 17 subjects, respectively; ii) of the 68 subjects with MBs, there are those with 28 lobar MBs (41%),

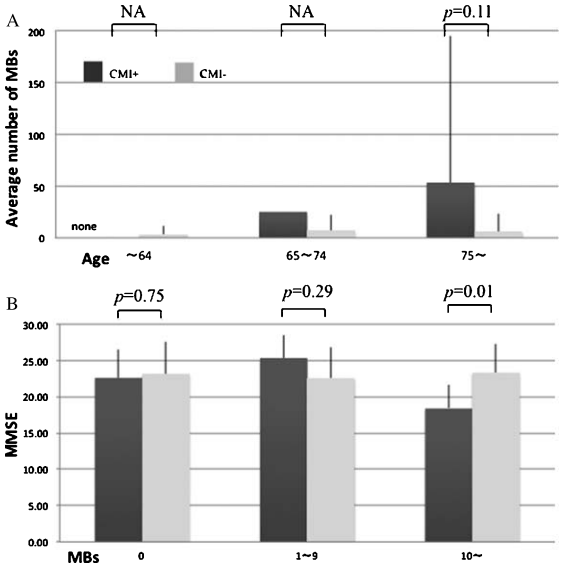

Fig. 4. Relationship between frequency of MBs and CMIs in each age (A) and their contribution to MMSE scores (B).

9 deep/infratentorial MBs (13%), and 31 mixed MBs (46%); iii) there is a numerical increase of MBs in CMI+ group especially in older ages; iv) in comparison between CMI+ and CMI– groups with mixed MBs, the former showed significantly worse scores in RCPM (score), TMT-A, category- and letter-word fluency, and copy and drawing of figures. The relatively small number of MBs at deep/infratentorial region may be attributable to the cohort specificity of memory clinic, which mostly consists of MCI and AD patients. It is noteworthy that the rate of the subjects with hyperlipidemia was significantly higher in the MBs– group, as compared to the MBs+ group, and may supplement inverse association between serum cholesterol and hemorrhagic stroke, especially with hypertension [30]. The subjects of the present study were quite different from our previous report [13], but the prevalence of CMI and MBs of both reports are similar ([13], CMI 13%, MBs 54%; the present study, CMI 16%, MBs 62%). The main difference of the results of the previous and the present study was that, in the present study, there were some subjects who possessed only CMIs without MB. In the previous report, all patients who possessed CMI also showed MBs. The reason for this difference might be caused by the difference of the clinical department. That is, the subjects of Ii's report [13] were recruited form outpatients who consulted with the Department of Neurology, whereas those of the present study where from a memory clinic.

The neuropsychological data have revealed that the MBs and CMIs contributed additively to cognitive impairment. The association between MB and cognition has already been shown by previous studies (e.g., [31–33]) and our results replicate these findings. Although analysis of the comparison between CMI+/MBs– and CMI–/MBs– showed significant differences on age, RCPM time, and WF (Category), analysis of the comparison between CMIs+/MBs+ and CMIs+/MBs– showed no significant difference on any neuropsychological assessments. Therefore, we may say that CMIs are a risk for cognitive dysfunction. There are several studies revealing a deteriorative effect of MBs on cognitive function. In population-based studies using SWI, MBs were detected in about 40% of people over 80 years of age [34] and correlated with lower scores on the MMSE [35]. In the Rotterdam Scan Study on non-demented community-resident people, more than five MBs revealed a relationship with decline in all cognitive function except for memory [33]. In the IAGES-Reykjavik study, multiple deep MBs were related to impairment of processing speed and executive function [31]. All these data indicate that MBs are related to executive dysfunction, the deterioration of psychomotor speed, and attention deficit [1]. The present study further confirmed a positive correlation between the number of MBs and frontal lobe dysfunction. The relationship between MBs and frontal dysfunction was already reported in the literature (e.g., frontal-executive impairment: [36]; attention: [37]). The underlying mechanisms of the pathological association between SVD and frontal dysfunction are unknown. However, for example, Van Norden et al. [37] discussed that histopathologic studies have shown that the presence of MB indicates widespread damage of arterioles by hypertension or by amyloid deposition as well as surrounding gliosis or even frank necrosis or infarction, resulting in microstructural damage of the surrounding white matter [38, 39]. In this way, MBs may disrupt white matter tracts relevant for cognitive function leading to damage to the neural networks superimposed to the effects of often co-occurring WML and lacunar infarcts.

On the contrary, it remains to be clarified whether CMIs are risk for dementia [4] based on the following reasons. First, evidence for the positive correlation has been based on retrospective clinic-pathological comparison and is endowed with anonymity [40]. Second, the frequency of CMIs has been shown to be relatively high even in non-demented people, and lastly, CMIs may accompany other vascular

lesions such as macro-infarction, lacunar infarction, and white matter lesions.

We applied exactly the same method by Ii et al., which makes feasible a sensitive detection of CMIs by 3D-FLAIR image and further identified cortical localization by DIR using 3D MRI [13] in the present study. It is reasonably concluded that the CMIs induce cognitive impairment, particularly related to frontal lobe dysfunction. In the elderly, CMIs have been mainly attributed to CAA [6]. To some extent, CAA is always present in AD brains and therefore, CMIs can be frequently observed in AD brains, especially in association with CAA [41]. As for the mechanisms of cognitive dysfunction, CMIs may directly damage the surrounding structures [42], but it is more likely that CMIs may represent an advanced stage of small vessel changes and its related blood-brain barrier disintegration and brain atrophy, because the observed finding for CMIs is only the tip of iceberg found in pathological specimens. In concert with this mechanism, Raman et al. reported that microinfarcts accelerated brain atrophy independent of AD pathology [43].

CMIs have been causatively related to CAA in demented patients. However, in the present study, CMIs frequently coexisted with mixed and multiple MBs, but not with pure lobar MBs. It is presumed that association of CMIs with mixed MBs represents relatively advanced SVD, which comprises two subtypes of SVD; i.e., hypertensive SVD and CAA with concordant progression [44]. This hypothesis appears to be underscored by a recent study in which both hypertensive SVD and CAA contributed to the pathogenesis of lobar MBs, at least in subjects with mixed MBs [45].

A large body of evidence has demonstrated correlation between frontal lobe dysfunction and hypertensive SVD [46, 47] and recently between those and CAA [48]. In the present study, CMIs, which may represent amyloid-related vasculopathy, coexisted frequently with mixed MBs, thereby suggesting that the both subtypes of SVD have contributed to impairment of executive function and word fluency.

This study has several limitations due to a relatively low detection rate of CMIs which was shown to be 17 of 109 (16%) in demented population. The rate was lower than 6 of 15 (40%) in demented brains with 7T MRI [14] and 24% (ranged between 3–43%) in pathological specimens [49], but higher than 6% in non-demented elderly patients with systolic hypertension with 3T MRI [15]. The low detection rate of CMIs made it difficult to accurately identify distribution of the whole CMIs and their contribution to cognitive impairment. Second, the effect of CMIs without MBs remains unclear. Among the 41 subjects without MBs, only five subjects possessed CMIs and were not suitable for statistical analysis. Lastly, the differential effect of CMIs was not identified among a variety of dementing illness, because most of the patients were categorized as having AD.

CONCLUSION

We carried out a series experiment using 3T MRI to memory clinic outpatients, in order to investigate the effects of MBs and CMIs on cognitive function. More MBs caused more severe cognitive impairment. The presence of CMIs might be an additional risk factor for dementia particularly of frontal lobe dysfunction. New imaging technique using 3T MRI combined with 3D FLAIR and DIR images is a useful tool to detect CMIs in clinical setting.

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SUPPLEMENTARY MATERIAL

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