

Cerebral Microbleeds Are Associated With Mild Cognitive Impairment in Patients With Hypertension

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Background—Cerebral microbleeds (CMBs) are hypothesized downstream markers of brain damage caused by vascular and amyloid pathologic mechanisms. The aim of this study was to determine whether CMB count and location are associated with an increased risk for mild cognitive impairment (MCI) in patients with essential hypertension without a history of transient ischemic attack or stroke.

Methods and Results—In this cross-sectional study, patients were prospectively enrolled from consecutive outpatients with essential hypertension 50 years and older at 3 centers in northern China. Generalized linear Poisson models were used to determine the association between the number and location of CMBs and MCI in patients with hypertension. The association of microbleeds with different cognitive domains was estimated using linear mixed models. The presence, number, and distribution of CMBs were greater in patients with hypertension who had MCI ($P < 0.001$). The presence of any CMBs, strictly lobar CMBs, and deep or infratentorial CMBs were all related to MCI after adjusting for age, sex, education, cardiovascular risk factors, body mass index, intima-media thickness, the presence of silent lacunar infarctions, white matter lesion grade, and brain atrophy. Furthermore, the presence of multiple microbleeds (≥ 5) was associated with lower Montreal Cognitive Assessment total scores and worse performance on specific domains of cognitive tests, such as global cognitive function, information processing speed, and motor speed.

Conclusions—This study suggests that the presence of and a greater number of cerebral CMBs independently correlate with MCI in patients with essential hypertension without a history of transient ischemic attack or stroke. (*J Am Heart Assoc.* 2018;7:e008453. DOI: 10.1161/JAHA.117.008453.)

Key Words: cerebral microbleed • cerebral small vessel disease • risk factor • hypertension • mild cognitive impairment

Mild cognitive impairment (MCI) is widely regarded as the intermediate stage of cognitive impairment between the changes seen in normal cognitive aging and those associated with dementia. Elderly patients with MCI constitute a high-risk population for developing dementia, particularly Alzheimer's disease (AD).¹ MCI has received considerable research attention for its potential importance in early identification and intervention for people with a risk for dementia.^{2,3}

Vascular pathology plays a prominent role in cognitive decline and dementia. Cerebral microbleeds (CMBs), as a form of cerebral small vessel disease, are reported to be highly prevalent in memory clinic patients and in patients with AD.^{4,5} Moreover, some studies have previously shown that the presence of numerous microbleeds, especially in a strictly lobar location, is associated with worse performance on tests that measure cognitive function.⁶ Growing evidence suggests that hypertension is the most powerful modifiable risk factor for cerebral vessel dysfunction and may contribute to consequent cognitive decline.^{7,8} Few studies have examined the relationship between CMBs and MCI in patients with hypertension. In the present study, we aimed to evaluate whether CMBs and, more specifically, CMB count and location are associated with an increased risk for MCI in patients with essential hypertension without a history of transient ischemic attack (TIA) or stroke.

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Materials and Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Clinical Perspective

What Is New?

- This study suggests that the presence of any cerebral microbleeds, strictly lobar cerebral microbleeds, and deep or infratentorial cerebral microbleeds were all related to mild cognitive impairment in patients with essential hypertension without a history of transient ischemic attack or stroke after adjusting for conventional risk factors.
- Furthermore, the presence of multiple microbleeds (≥ 5) was associated with lower Montreal Cognitive Assessment total scores and worse performance on specific domains of cognitive tests, such as global cognitive function, information processing speed, and motor speed.

What Are the Clinical Implications?

- Our findings suggest that the presence and greater number of cerebral microbleeds independently correlate with mild cognitive impairment in patients with essential hypertension without a history of transient ischemic attack or stroke.

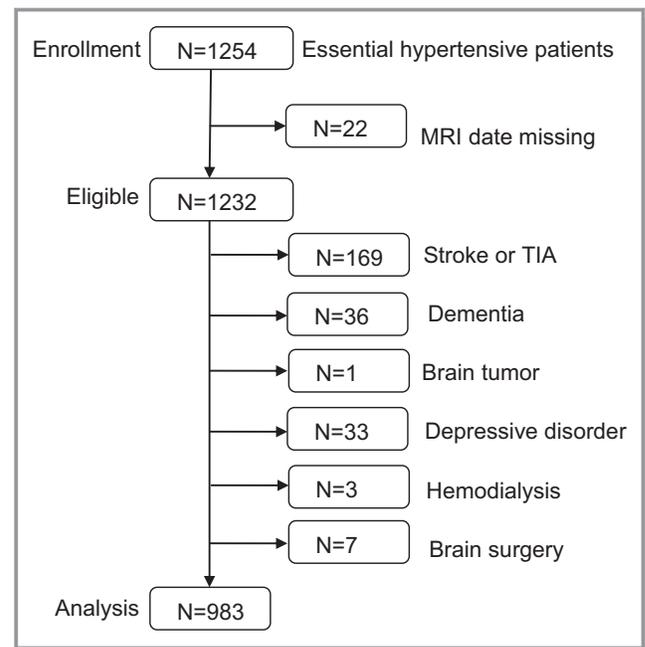


Figure 1. Description of the study population. MRI indicates magnetic resonance imaging; TIA, transient ischemic attack.

Study Population

Participants were prospectively enrolled from consecutive outpatients with essential hypertension 50 years and older who visited the Department of Neurology between December 2015 and December 2016 at 3 centers in northern China. All patients were entered in a prospective electronic database and underwent a standardized interview and physical examination. Hypertension was defined as blood pressure (BP) $\geq 140/90$ mm Hg at 3 different times or the use of antihypertensive medications. Carotid intima-media thickness (IMT) was measured to reflect the severity of atherosclerosis, and magnetic resonance imaging (MRI) was performed to evaluate suspicious neurological symptoms (ie, headache or dizziness, vertigo, numbness, syncope, or subjective memory impairment). When neither neurological symptoms nor a history of stroke or TIA were identified, the patient was considered eligible for the study.

During the study period, 1254 patients with essential hypertension were identified as candidates (Figure). We then excluded 22 patients whose MRI examinations were not completed. Patients with a history of stroke or TIA ($n=169$), dementia ($n=36$), brain tumor ($n=1$), or depressive disorder ($n=33$) or those undergoing hemodialysis ($n=3$) or brain surgery ($n=7$) were excluded to eliminate any effects of clinically evident diseases on CMBs.

The study followed the Declaration of Helsinki and was approved by the ethics committee of Weihai Municipal Hospital, and all patients provided written informed consent before inclusion.

Diagnosis of MCI

The clinical diagnosis of MCI was made according to the established Petersen criteria,¹ including subjective complaints of memory deficits, abnormal memory functioning for age, the absence of dementia according to a diagnostic examination (Clinical Dementia Rating <0.5), and normal everyday functioning on the activities of daily living scale. Patients with MCI with depressive disorder were excluded.⁹ After enrollment, cognitive function was evaluated by a Chinese-version questionnaire of the Montreal Cognitive Assessment¹⁰ the Letter Digit Substitution Task, Word Fluency Test, Purdue Pegboard Test, 15-Word Verbal Learning Test, and Stroop test.¹¹ Z scores (individual test score minus the mean test score divided by the SD) were generated for each cognitive test, except for the Montreal Cognitive Assessment. We computed compound scores for global cognition (the mean Z score of the Letter Digit Substitution Task, Stroop interference subtask, Word Fluency Test, delayed recall of the 15-Word Verbal Learning Test, and Purdue Pegboard Test), memory (the mean Z score of immediate and delayed recall of the 15-Word Verbal Learning Test), information processing speed (the mean Z score of the Stroop reading and color naming subtasks and Letter Digit Substitution Task), executive functioning (the mean Z score of the Letter Digit Substitution Task, Stroop interference subtask, and Word Fluency Test), and motor speed (the mean Z score of the Purdue Pegboard Test). The neuropsychological tests were administered in a quiet, well-lit room and under standard circumstances by trained examiners.

Brain MRI Data

All 983 participants with hypertension underwent MRI examinations with susceptibility-weighted imaging. In addition, all patients received conventional T1- and T2-weighted, diffusion-weighted imaging scans and fluid-attenuated inversion recovery sequence imaging. MRI examinations were performed with a Magnetom Trio whole-body 3.0-T MRI scanner (Siemens) with a 40-mT/m gradient. A receiver-only 8-channel phased-array head coil was used in all acquisitions with an integrated parallel acquisition technique. Susceptibility-weighted imaging was acquired as a fully velocity compensated, 3-dimensional gradient echo sequence using the following parameters: repetition time, 27 ms; time of echo, 20 ms; flip angle, 15°; matrix, 350×445; field of view, 192×220 mm; and slice thickness, 1.2 mm. Minimal intensity projection images were reconstructed on a console by overlaying the 6 adjacent slices from the original susceptibility-weighted imaging, with a slice thickness of 7.2 mm.^{12,13} CMBs were defined as focal areas with very low signal intensity, <10 mm.¹⁴ Hypointense lesions were excluded if they appeared to be vascular flow voids (based on sulcal location or linear shape), basal ganglia mineralization, or artifacts from an adjacent bone or sinus. The presence and number of CMBs on susceptibility-weighted imaging were independently interpreted by 2 experienced neuroradiologists and determined by consensus. CMBs were classified manually as lobar CMBs with or without cerebellar CMBs (suggestive of cerebral amyloid angiopathy) and deep or infratentorial CMBs with or without lobar CMBs (suggestive of hypertensive arteriopathy).¹⁵

The interrater reliability for the whole group for the presence of CMBs was $\kappa=0.824$ and the intraclass correlation coefficient for the number of CMBs was $\kappa=0.871$, which indicates good agreement.

A white matter lesion (WMH) was defined as at least 1 focal lesion in the cerebral white matter with corresponding hyperintensity on fluid-attenuated inversion recovery images. The Fazekas scale was used to score the white matter lesions. Scores of 0 to 2 were given for 3 periventricular hyperintensities (PVH; range: 0–6) and scores of 0 to 6 were given for a deep WMH (DWMH) in the temporal, frontal, parietal, or occipital lobe (DWMH; range: 0–24).¹⁶

Silent lacunar infarctions (SLIs) were defined as focal lesions >3 mm and <15 mm, with a hyperintense rim on fluid-attenuated inversion recovery images, corresponding hyperintensity on T2-weighted images, and corresponding hypointensity on T1-weighted images.

Brain atrophy was defined as total brain tissue volume expressed as percentage of intracranial volume. Total brain volume and intracranial volume were calculated on the axial T1-weighted inversion recovery and FLAIR images of all participants using the k-nearest neighbor-based probabilistic segmentation.¹⁷

Other Measurements

The diagnosis of diabetes mellitus was based on repeated pathologic blood tests indicating fasting values ≥ 126 mg/dL or value loads ≥ 200 mg/dL 2 hours after oral glucose administration or the use of antidiabetic treatment. Hyperlipidemia was determined when total cholesterol was ≥ 200 mg/dL or when low-density lipoprotein cholesterol was ≥ 130 mg/dL. Alcohol was accepted as a risk factor if current consumption reached 300 g/wk. A history of smoking was coded if the patient smoked during the 3 months before the most recent stroke event. Total protein, serum albumin, total cholesterol, triglycerides, low-density lipoprotein cholesterol, serum urea nitrogen, and hemoglobin levels were measured by standard laboratory methods. Body mass index (BMI) was also calculated.

Color Doppler ultrasound was used to locate the thickest site of the carotid artery intima-media and to measure the thickness at this site, 2 upstream sites, and 1 site that was 1 cm downstream, each of which were measured 6 times to obtain average values.

Statistical Analysis

SPSS version 13.0 statistical software (SPSS Inc) was used for the statistical analysis. Tests for the homogeneity of variances were performed. The Kolmogorov–Smirnov test was also performed to ascertain the normality of the distribution of continuous variables. The normally distributed measurement data were represented as the mean \pm SD ($\bar{x}\pm$ SD) and the results of the 2 groups were compared using a *t* test. The counting data were represented as a ratio and the results of the 2 groups were compared using χ^2 test. Generalized linear Poisson models were used to investigate the distributional patterns of CMBs relative to MCI in patients with hypertension without a history of TIA or stroke. Linear mixed models with added random effects were used to determine the relationship between CMB count per topographic distribution in the brain and cognitive decline in specific domains. Differences with a *P*<0.05 were considered statistically significant.

Results

Characteristics of the Sample

Among 983 patients with hypertension, 164 patients had a clinical diagnosis of MCI. CMBs were detected in 215 patients with hypertension (21.9%). Of the 1062 identified CMBs, 285 (26.8%) were located in the basal ganglia, 154 (14.5%) in the thalamus, 151 (14.2%) in the brainstem (mostly in the pons), 120 (11.3%) in the cerebellum, 236 (22.2%) in the subcortical white matter or periventricular white matter, and 116 (10.9%) in the cortex. In the univariate analysis, age, the degrees of

PVH and DWMH, and the prevalence of SLIs were higher in patients with hypertension with MCI. The total brain volume/intracranial volume ratio was lower in patients with hypertension with MCI than in those without MCI ($P<0.032$). Furthermore, the presence, number, and distribution of CMBs

were greater in patients with hypertension and MCI ($P<0.001$) (Table 1).

We assessed the use of medications in all enrolled patients. The results indicate no significant differences in medication use between the groups (Table 1).

Table 1. Demographic and Clinical Characteristics of Enrolled Patients With Hypertension Without and With MCI

Characteristics	All Patients (N=983)	No MCI (n=819)	MCI (n=164)	P Value
Age, y	64.38±8.26	64.38±8.26	65.52±8.85	0.13
Men, No. (%)	539 (54.8)	452 (55.2)	87 (53.0)	0.34
DM, No. (%)	168 (17.1)	138 (16.8)	30 (18.3)	0.36
Education, mean±SD, y	7.6±4.3	7.9±4.7	7.0±4.1	0.11
Hyperlipidemia, No. (%)	543 (55.2)	451 (55.1)	92 (56.1)	0.44
Current smoker, No. (%)	162 (16.5)	129 (15.8)	33 (20.1)	0.11
Current drinker, No. (%)	221 (22.5)	186 (22.7)	35 (21.3)	0.39
Duration of hypertension, mean±SD, mo	61.7±17.3	59.9±16.8	63.2±18.4	0.27
SBP, mm Hg	139±18	138±16	144±21	0.12
DBP, mm Hg	82±13	80±12	84±14	0.21
Pulse pressure, mm Hg	61±6	60±5	63±8	0.14
Use of antihypertensive drugs, No. (%)	535 (54.4)	451 (52.9)	84 (51.2)	0.21
Calcium channel blockers, No. (%)	319 (32.5)	272 (33.2)	47 (28.7)	0.15
ACEI/ARB, No. (%)	419 (42.6)	351 (42.9)	68 (41.5)	0.41
β-Blockers, No. (%)	183 (18.6)	159 (19.4)	24 (14.6)	0.09
Diuretics, No. (%)	137 (13.9)	116 (14.2)	21 (12.8)	0.38
Use of antithrombotic drugs, No. (%)	202 (20.5)	165 (20.2)	37 (22.6)	0.27
Use of lipid-lowering drugs, No. (%)	332 (33.8)	281 (34.3)	51 (31.1)	0.24
FBG, mg/dL	115.16±21.78	111.45±20.38	117.73±22.91	0.39
TC, mg/dL	175.61±27.18	171.32±25.61	179.24±29.17	0.34
LDL, mg/dL	129.83±31.42	126.58±28.17	131.18±32.72	0.27
Hemoglobin, g/L	139.27±10.18	142.34±11.11	136.55±9.87	0.35
BMI, kg/m ²	24.78±5.14	23.98±5.52	25.29±6.71	0.23
IMT, mm	1.13±0.24	1.10±0.19	1.15±0.25	0.14
BUN, mg/dL	58.62 ±28.13	53.15±25.26	62.15±29.54	0.21
SLI, No. (%)	459 (46.7)	365 (44.6)	94 (57.3)	0.002
PVH, median (IQR)	2 (1–5)	2 (1–3)	3 (2–6)	0.007
DWMH, median (IQR)	5 (2–10)	4 (1–8)	7 (3–11)	0.003
Brain atrophy, mean±SD	0.820±0.025	0.827±0.027	0.814±0.022	0.032
Presence of CMBs, No. (%)	215 (21.9)	106 (12.9)	109 (66.5)	<0.001
No. of CMBs, median (IQR)	0 (0–0)	0 (0–0)	9 (0–19)	<0.001
Distribution of CMBs, No. (%)				
Lobar	67 (6.8)	35 (4.3)	32 (19.5)	<0.001
Deep or infratentorial	148 (15.1)	71 (8.7)	77 (47.0)	

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, serum urea nitrogen; CMBs, cerebral microbleeds; DBP, diastolic blood pressure; DM, diabetes mellitus; DWMH, deep white matter hyperintensities; FBG, fasting blood glucose; IMT, intima-media thickness; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; MCI, mild cognitive impairment; PVH, periventricular hyperintensities; SBP, systolic blood pressure; SLI, silent lacunar infarction; TC, total cholesterol.

Adjusted Relationship Between the Number and Location of CMBs and MCI in Patients With Hypertension

Generalized linear Poisson models were used to determine the association between the number and location of CMBs and MCI in patients with hypertension, as shown in Table 2. The total number of CMBs and presence of ≥ 5 CMBs were all related to MCI (odds ratio [OR], 1.66 [$P=0.019$]; OR, 2.45 [$P=0.017$], respectively) after adjusting for age, sex, education, diabetes mellitus, hyperlipidemia, current smoker, current drinker, BP levels, BMI, IMT, presence of SLI, WMH (PVH, DWMH) grade, and brain atrophy (model 2). No significant correlations were found between the presence of 1 and 2 to 4 CMBs and MCI after adjusting for confounders. For CMB location, the presence of any CMBs, lobar CMBs, and deep or infratentorial CMBs were all related to MCI (OR, 2.18 [$P=0.024$]; OR, 1.55 [$P=0.028$]; OR, 2.74 [$P=0.019$], respectively) after adjusting for age, sex, education, diabetes mellitus, hyperlipidemia, current smoker, current drinker, BP levels, BMI, IMT, presence of SLI, WMH (PVH, DWMH) grade, and brain atrophy (model 2). Generalized linear Poisson models also found the presence of cerebellar CMBs was related to MCI (OR, 1.41 [$P=0.043$]) after adjusting for these confounders.

Association Between Deep or Infratentorial CMBs and Performance on Cognitive Tests in Patients With Hypertension

Table 3 shows the association of deep or infratentorial CMBs with performance on cognitive tests in patients with hypertension and MCI. The number of deep or infratentorial CMBs

per SD increase was significantly related to lower MoCA total scores and worse performance on tests of motor speed. Compared with no microbleeds, the presence of numerous (≥ 5) CMBs was significantly associated with lower MoCA total scores and with worse performance on tests of global cognitive function, information processing speed, executive function, and motor speed, but not with memory performance (model 0 in Table 3). Additional adjustments for age and sex did not change these results (model 1 in Table 3). Statistical significance remained for the association between (numerous) microbleeds and lower MoCA total scores and worse performance on global cognitive function, information processing speed, and motor speed upon adjusting for age, sex, education, diabetes mellitus, hyperlipidemia, current smoker, current drinker, BP levels, BMI, IMT, presence of SLI, WMH (PVH, DWMH) grade, and brain atrophy (model 2 in Table 3).

Association Between Lobar CMBs and Performance on Cognitive Tests in Patients With Hypertension

Table 4 shows the association of strictly lobar CMBs with performance on cognitive tests in patients with hypertension with MCI. Per SD increase, a higher CMB number was significantly associated with lower MoCA total scores and worse performance on tests of information processing speed. When analyzed per category, the presence of numerous (≥ 5) CMBs was significantly associated with lower MoCA total scores and with worse performance on tests of global cognitive function, memory, information processing speed, executive function, and motor speed (model 0 in Table 4). Additional adjustments for age and sex did not change these

Table 2. CMBs Distributional Pattern Relevant to MCI in Patients With Hypertension

	Model 0		Model 1		Model 2	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
CMB No.						
Total No.	2.81 (1.73–3.91)	0.001	2.67 (1.35–3.75)	0.005	1.66 (1.15–2.78)	0.019
1 vs none	1.30 (0.81–2.14)	0.109	1.24 (0.75–2.08)	0.142	1.09 (0.65–1.82)	0.288
2 to 4 vs none	1.61 (0.91–3.32)	0.037	1.38 (0.71–2.94)	0.071	1.14 (0.74–2.91)	0.181
≥ 5 vs none	5.47 (2.06–11.42)	<0.001	4.53 (1.85–11.31)	0.004	2.45 (1.35–9.54)	0.017
CMB location						
Any CMBs	9.91 (3.14–15.71)	<0.001	7.17 (2.73–12.32)	0.001	2.18 (1.33–4.86)	0.024
Lobar	4.39 (2.15–9.43)	<0.001	3.59 (1.24–6.23)	0.011	1.55 (0.81–3.22)	0.028
Deep or infratentorial	8.12 (4.62–13.27)	<0.001	5.33 (2.57–10.69)	0.006	2.74 (1.24–4.78)	0.019

Model 0: unadjusted. Model 1: adjusted for age, sex. Model 2: adjusted for age, sex, education, diabetes mellitus, hyperlipidemia, current smoker, current drinker, blood pressure, body mass index, intima-media thickness, presence of silent lacunar infarction, white matter hyperintensities (periventricular hyperintensities, deep white matter hyperintensities) grade, and brain atrophy. CI indicates confidence interval; CMB, cerebral microbleed; OR, odds ratio; MCI, mild cognitive impairment.

Table 3. Association Between Deep or Infratentorial CMBs and Performance on Cognitive Tests in Patients With Hypertension

	Difference in Test Scores (95% CI)						
	MoCA Scores	Z Score Global Cognitive Function	Z Score Memory	Z Score Information Processing Speed	Z Score Executive Function	Z Score Motor Speed	
CMB No., per SD increase, Model 0	-0.12 (-0.34 to 0.14) [†]	-0.04 (-0.06 to 0.03)	-0.03 (-0.06 to 0.03)	-0.01 (-0.06 to 0.05)	-0.03 (-0.11 to 0.12)	-0.10 (-0.35 to 0.11) [†]	
1 vs none, model 0	-0.03 (-0.12 to 0.12)	0.04 (-0.04 to 0.14)	0.05 (-0.10 to 0.23)	0.06 (-0.09 to 0.13)	0.03 (-0.08 to 0.13)	0.12 (-0.06 to 0.23)	
2 to 4 vs none, model 0	-0.14 (-0.41 to 0.07)	-0.04 (-0.13 to 0.12)	-0.01 (-0.16 to 0.19)	-0.04 (-0.12 to 0.10)	-0.06 (-0.17 to 0.10)	-0.19 (-0.94 to 0.15)	
≥5 vs none, model 0	-0.69 (-1.61 to -0.13) [*]	-0.41 (-1.45 to -0.09) [*]	-0.15 (-0.34 to 0.11)	-0.34 (-0.55 to -0.11) [†]	-0.28 (-0.46 to 0.02) [†]	-0.71 (-1.66 to -0.13) [*]	
CMB No., per SD increase, model 1	-0.07 (-0.29 to 0.12) [†]	-0.02 (-0.05 to 0.03)	-0.04 (-0.05 to 0.04)	-0.02 (-0.07 to 0.03)	-0.04 (-0.15 to 0.11)	-0.10 (-0.31 to 0.11) [†]	
1 vs none, model 1	-0.02 (-0.12 to 0.11)	0.06 (-0.07 to 0.13)	0.06 (-0.11 to 0.28)	0.09 (-0.10 to 0.14)	0.04 (-0.07 to 0.16)	0.11 (-0.06 to 0.22)	
2 to 4 vs none, model 1	-0.14 (-0.40 to 0.08)	-0.04 (-0.10 to 0.13)	-0.03 (-0.19 to 0.20)	-0.03 (-0.12 to 0.10)	-0.04 (-0.19 to 0.17)	-0.21 (-0.89 to 0.13)	
≥5 vs none, model 1	-0.67 (-1.65 to -0.12) [*]	-0.41 (-1.42 to -0.08) [*]	-0.19 (-0.33 to 0.11)	-0.35 (-0.57 to -0.13) [†]	-0.26 (-0.41 to 0.06) [†]	-0.68 (-1.63 to -0.13) [*]	
CMB No., per SD increase, model 2	-0.04 (-0.14 to 0.07)	-0.02 (-0.06 to 0.03)	-0.01 (-0.06 to 0.04)	0.02 (-0.05 to 0.10)	-0.02 (-0.14 to 0.12)	-0.06 (-0.20 to 0.11)	
1 vs none, model 2	-0.00 (-0.08 to 0.09)	0.07 (-0.05 to 0.10)	0.07 (-0.09 to 0.28)	0.08 (-0.07 to 0.21)	0.03 (-0.07 to 0.13)	0.12 (-0.07 to 0.26)	
2 to 4 vs none, model 2	-0.06 (-0.31 to 0.07)	-0.01 (-0.08 to 0.17)	0.04 (-0.16 to 0.23)	-0.01 (-0.11 to 0.14)	-0.03 (-0.16 to 0.20)	-0.13 (-0.39 to 0.09)	
≥5 vs none, model 2	-0.32 (-1.14 to 0.06) [†]	-0.23 (-1.07 to 0.05) [†]	-0.07 (-0.25 to 0.21)	-0.23 (-0.45 to -0.06) [†]	-0.07 (-0.22 to 0.25)	-0.43 (-1.31 to -0.08) [†]	

Model 0: unadjusted. Model 1: adjusted for age, sex. Model 2: adjusted for age, sex, education, diabetes mellitus, hyperlipidemia, current smoker, current drinker, blood pressure, body mass index, intima-media thickness, presence of silent lacunar infarction, white matter hyperintensities (periventricular hyperintensities), grade, and brain atrophy. CI indicates confidence interval; CMB, cerebral microbleed; MoCA, Montreal Cognitive Assessment.

^{*} $P<0.01$; [†] $P<0.05$.

Table 4. Association Between Lobar CMBs and Performance on Cognitive Tests in Patients With Hypertension

	Difference in Test Scores (95% CI)					
	MoCA Scores	Z Score Global Cognitive Function	Z Score Memory	Z Score Information Processing Speed	Z Score Executive Function	Z Score Motor Speed
CMB No., per SD increase, model 0	-0.09 (-0.17 to 0.05) [†]	-0.03 (-0.11 to 0.04)	-0.03 (-0.14 to 0.09)	-0.07 (-0.14 to 0.02) [†]	-0.03 (-0.06 to 0.05)	-0.03 (-0.15 to 0.04)
1 vs none, model 0	-0.02 (-0.16 to 0.14)	0.00 (-0.12 to 0.09)	0.00 (-0.08 to 0.08)	0.02 (-0.07 to 0.12)	-0.01 (-0.10 to 0.09)	0.03 (-0.08 to 0.10)
2 to 4 vs none, model 0	-0.16 (-0.47 to 0.09)	-0.03 (-0.16 to 0.11)	-0.02 (-0.12 to 0.10)	-0.12 (-0.33 to 0.13)	-0.14 (-0.37 to 0.14)	-0.06 (-0.18 to 0.14)
≥5 vs none, model 0	-0.60 (-1.52 to -0.12) [*]	-0.37 (-0.79 to 0.02) [†]	-0.36 (-0.77 to 0.06) [†]	-0.73 (-1.67 to -0.11) [*]	-0.34 (-0.65 to -0.08) [†]	-0.29 (-0.51 to -0.08) [†]
CMB No., per SD increase, model 1	-0.08 (-0.12 to 0.09) [†]	-0.03 (-0.09 to 0.03)	-0.01 (-0.13 to 0.07)	-0.08 (-0.14 to 0.03) [†]	-0.03 (-0.09 to 0.06)	-0.04 (-0.14 to 0.05)
1 vs none, model 1	-0.04 (-0.17 to 0.13)	0.00 (-0.08 to 0.07)	0.00 (-0.08 to 0.10)	0.01 (-0.06 to 0.13)	-0.01 (-0.07 to 0.08)	0.03 (-0.09 to 0.16)
2 to 4 vs none, model 1	-0.15 (-0.43 to 0.09)	-0.03 (-0.16 to 0.11)	-0.02 (-0.14 to 0.11)	-0.11 (-0.26 to 0.11)	-0.12 (-0.44 to 0.14)	-0.06 (-0.19 to 0.13)
≥5 vs none, model 1	-0.51 (-1.47 to -0.06) [†]	-0.35 (-0.81 to 0.02) [†]	-0.33 (-0.85 to 0.03) [†]	-0.73 (-1.65 to -0.11) [*]	-0.33 (-0.58 to -0.09) [†]	-0.27 (-0.44 to -0.09) [†]
CMB No., per SD increase, model 2	-0.03 (-0.07 to 0.04)	-0.01 (-0.04 to 0.02)	-0.01 (-0.12 to 0.09)	-0.06 (-0.13 to 0.09) [†]	-0.01 (-0.06 to 0.04)	-0.01 (-0.11 to 0.06)
1 vs none, model 2	-0.04 (-0.15 to 0.12)	0.00 (-0.05 to 0.07)	0.00 (-0.07 to 0.09)	0.03 (-0.05 to 0.11)	0.00 (-0.07 to 0.08)	0.03 (-0.06 to 0.17)
2 to 4 vs none, model 2	-0.12 (-0.44 to 0.10)	-0.02 (-0.11 to 0.07)	-0.01 (-0.11 to 0.09)	-0.09 (-0.21 to 0.08)	-0.06 (-0.26 to 0.05)	-0.04 (-0.15 to 0.13)
≥5 vs none, model 2	-0.36 (-1.19 to 0.05) [†]	-0.23 (-0.42 to -0.06) [†]	-0.17 (-0.47 to 0.07)	-0.43 (-1.36 to -0.09) [†]	-0.13 (-0.35 to -0.02)	-0.11 (-0.33 to -0.05)

Model 0: unadjusted. Model 1: adjusted for age, sex. Model 2: adjusted for age, sex, education, diabetes mellitus, hyperlipidemia, current smoker, current drinker, blood pressure, body mass index, intima-media thickness, presence of silent lacunar infarction, white matter hyperintensities (periventricular hyperintensities, deep white matter hyperintensities) grade, and brain atrophy. CI indicates confidence interval; CMB, cerebral microbleed; MoCA, Montreal Cognitive Assessment

**P*<0.01; [†]*P*<0.05.

results (Model 1 in Table 4). When additionally adjusting for confounders, including age, sex, education, diabetes mellitus, hyperlipidemia, current smoker, current drinker, BP levels, BMI, IMT, presence of SLI, WMH (PVH, DWMH) grade, and brain atrophy (model 2 in Table 4), the presence of ≥ 5 lobar CMBs remained associated with lower MoCA total scores and with worse performance on global cognitive function and information processing speed (model 2 in Table 4). No significant correlations were found between the presence of 1 or 2 to 4 lobar CMBs and MoCA total scores or compound scores of neuropsychological tests of specific cognitive domains in patients with hypertension.

Discussion

In the present study, we investigated the association between CMBs and MCI in 983 patients with hypertension at 3 centers in northern China. Based on the results from this study, the rate of CMBs in patients with hypertension was 21.9%. Our results are consistent with those of previous studies.¹⁸ The presence, number, and distribution of CMBs were greater in patients with hypertension with MCI than in those without MCI. Generalized linear Poisson models showed that the total number of CMBs and the presence of ≥ 5 CMBs were all related to MCI after adjusting for age, sex, education, diabetes mellitus, hyperlipidemia, current smoker, current drinker, BP levels, BMI, IMT, presence of SLI, WMH (PVH, DWMH) grade, and brain atrophy. The presence of any CMBs, strictly lobar CMBs, and deep or infratentorial CMBs were all related to MCI after adjusting for confounders. Furthermore, the presence of multiple microbleeds (≥ 5) is associated with lower MoCA total scores and with worse performance on specific domains of cognitive tests, such as global cognitive function, information processing speed, and motor speed. To the best of our knowledge, no previous studies have investigated the association between CMBs and MCI in patients with essential hypertension without a history of TIA or stroke.

Previous cross-sectional and longitudinal studies^{6,19,20} in healthy adults also demonstrated that CMBs, especially in large numbers, are related to lower Mini-Mental State Examination scores, worse information processing, and worse executive functioning. Other studies also found that CMBs were associated with cognitive decline in patients with ischemic stroke or TIA and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.^{21–23}

The pathological differences in CMBs according to distribution is now well-known, with CMBs in deep or infratentorial regions considered to be associated with hypertensive microangiopathy, whereas strictly lobar CMBs are considered attributable to neurodegenerative pathology and cerebral amyloid angiopathy.²⁴ Recent studies in experimental models have shown that hypertension promotes β -secretase activity

and increases cerebral vascular amyloid deposits and that hypertension-mediated impairment of vascular repair mechanisms may contribute to the faster development of neuropathology and cognitive deficits in experimental models of AD.^{25,26} CMBs were postulated as the potential “missing link” in the interaction between cerebral amyloid angiopathy and hypertensive arteriolosclerosis in the pathogenesis of AD.²⁷ The robust associations we assessed between the presence and number of cerebral CMBs and cognitive function further support this notion.

Mechanisms by which CMBs influence cognitive function remain speculative and may be causal or noncausal.²⁸ CMBs may represent a proxy measure of cerebral vascular disease overall, and their presence may influence cognition indirectly. This hypothesis is supported by our findings because we found associations with multiple CMBs in widespread areas rather than with single or multiple CMBs clustered in a specific brain region. However, histopathologic studies have shown that the presence of CMBs indicates widespread damage in arterioles by hypertension, amyloid deposition and surrounding gliosis, infarction, or even necrosis, resulting in microstructural damage of the surrounding white matter.^{29,30} Therefore, CMBs may disrupt white matter tracts involved in cognitive function, leading to damage to the neural networks superimposed by the effects of frequently co-occurring white matter lesions and lacunar infarctions. This tissue damage, which is not visible on conventional MRI, can be assessed in future studies with new techniques such as diffusion tensor imaging or resting state MRI. We found that CMBs were related to cognitive performance independent of age, sex, education, major cardiovascular factors, WMHs, and SLI. This finding, together with results from pathological studies showing that CMBs are frequently characterized by surrounding microstructural damage,³⁰ suggests that CMBs have a direct effect on cognitive performance rather than simply reflecting the presence of other markers of cerebral small vessel disease because our findings were independent of the presence of WMHs and SLI.

We observed an association between lobar and deep or infratentorial CMBs and decline in information processing speed, but not in declarative memory. Information processing speed tasks may be the most sensitive to vascular pathology.^{31,32} Furthermore, accelerated decline in information processing function may be a harbinger for future decline in cognition related to AD. Notably, among cognitively normal adults older than 60 years, fibrillar forms of β -amyloid were related to reductions in measures of processing speed, but not declarative memory, a hallmark feature of AD.³³ In our study, we found an association between lobar (suggestive of cerebral amyloid angiopathy) and deep or infratentorial CMBs (suggestive of hypertensive arteriopathy) and performance reductions in speed tasks in patients with essential

hypertension. Our study emphasizes the role of vascular disease in the pathogenesis of cognitive impairment. Accumulating evidence suggests that vascular damage may be particularly important in the initiation of neurodegenerative disease.^{34,35}

Study Limitations

Our study has some limitations. First, the present investigation was a cross-sectional study. We need to conduct a longitudinal study to validate the causal relationship between CMBs and MCI. Second, our results are limited to the cohort of elderly individuals with hypertension; therefore, they cannot be generalized to the general population. Third, we were unable to characterize the precise cause of cognitive impairment using molecular ligands (eg, β -amyloid) or pathological confirmation.

Conclusions

We found that the presence and greater number of cerebral CMBs independently correlate with MCI in patients with essential hypertension without a history of TIA or stroke, and that this relationship is driven not only by strictly lobar CMBs but also by deep or infratentorial CMBs. These results suggest that CMBs are clinically not as silent as they have been considered to be, which may help us understand the role of vascular disease in cognitive decline. Studies with longitudinal follow-up should identify whether the presence at baseline and/or increases in CMBs over time can predict the future development of dementia.

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Disclosures

None.

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