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Deep cerebral microbleeds are associated with the severity of lacunar infarcts and hypertension

A retrospective analysis

Zhongbao Gao, MD, PhD[a,c], Yongzhi Zhai, MD, PhD[b], Xingli Zhao, BSN[c], Wei Wang, MD, PhD[c], Weiping Wu, MD, PhD[c], Zhenfu Wang, MD, PhD[c], Ruozhuo Liu, MD, PhD[d], Xiaodan Wang, MD, PhD[a,*]

Abstract

Cerebral microbleeds (CMBs) and lacunar infarcts are common manifestations of cerebral small vessel disease. However, the association between the location of CMBs and lacunar infarcts is unclear. Our study aimed to clarify the relationship between the location of CMBs and lacunar infarcts.

This study retrospectively analyzed 166 patients with ischemic stroke or transient ischemic attacks admitted in the Geriatric Neurology Department of Chinese PLA General Hospital between February 2010 and December 2012. We collected clinical characteristics and risk factors of CMBs. The location of CMBs on T2*-weighted angiography was assessed by the Microbleed Anatomical Rating Scale. The number of lacunar infarcts and the severity of white matter hyperintensities were also recorded. The association between the location of CMBs and lacunar infarcts parameters was examined.

CMBs were present in 77 (46.4%) patients. The presence [odds ratios (OR), 2.14; 95% confidence interval (CI), 1.02–4.48], number (OR, 1.17; 95% CI, 1.02–1.36 per lesion), severity (OR, 1.61; 95% CI, 1.07–2.42) of lacunar infarcts, and hypertension (OR, 5.76; 95% CI, 2.01–16.55) were independent risk factors for CMBs. Stratified by the location of CMBs, lobar CMBs and infratentorial CMBs did not show significant association with lacunar infarcts. Deep CMBs were significantly associated with the number (OR 1.18, 95% CI 1.03–1.36) and severity (OR 1.71, 95% CI 1.11–2.63) of lacunar infarcts. Moreover, the percentage of deep CMBs increased with the increased severity of lacunar infarcts ($P = .003$).

Deep CMBs rather than lobar and infratentorial CMBs are associated with lacunar infarcts.

Abbreviations: CI = confidence interval, CMBs = cerebral microbleeds, DWMH = deep white-matter hyperintensities, FLAIR = fluid - attenuated inversion recovery, GRE = gradient-recalled-echo, MRI = magnetic resonance imaging, OR = odds ratios, PVH = peri-ventricular hyperintensities, TIA = transient ischemic attack.

Keywords: cerebral microbleeds, cerebral small vessel disease, hypertension, lacunar infarcts

1. Introduction

Cerebral microbleeds (CMBs) are homogeneous, small, round foci of low signal loss on T2*-weighted gradient-recalled-echo (GRE) sequence of magnetic resonance imaging (MRI).[1,2] They are focal deposits of hemosiderin in the brain which is caused by a previous leakage of blood from small vessels.[3] Generally, CMBs are considered to be clinically correlated with aging, chronic hypertension, and white matter hyperintensities [4–6]. Further, different types of CMBs refer to different mechanisms. CMBs located in the deep white matter are associated with hypertensive vasculopathy, whereas those in the lobe are more likely associated with cerebral amyloid angiopathy.[4] A recent report shows that lobar, but not deep or infratentorial, CMBs are associated with changes in cognitive function, especially in visuospatial executive functions.[7]

Lacunar infarcts are small noncortical infarcts caused by occlusion of a single penetrating branch of a large cerebral artery. CMBs and lacunar infarcts are common manifestations of cerebral small vessel disease. They are particularly observed on MRI in the elderly and in patients with cerebrovascular diseases. The association between CMBs and lacunar infarcts has already been reported not only in those with ischemic stroke,[8,9] but also in healthy subjects.[10] A recent report showed that lacunar infarcts were associated with deep or infratentorial CMBs.[11] However, the association between CMBs location and lacunar infarcts severity is unclear. Therefore, the present study aimed to study the possible links between the location of CMBs and the presence and severity of lacunar infarcts in patients with ischemic stroke and transient ischemic attack (TIA).

2. Materials and methods

2.1. Patients

We retrospectively recruited 166 patients with ischemic stroke or TIA who were consecutively admitted to the Geriatric Neurology

Department of Chinese PLA General Hospital, China between February 2010 and December 2012. Of these patients, 134 were diagnosed with ischemic stroke, and 32 were diagnosed with TIA. Written informed consent was obtained from all the participants. The study design was approved by the Ethics Committee of PLA General Hospital.

2.2. Vascular risk factors

We recorded information on the following vascular risk factors: age, sex, hypertension, diabetes mellitus and history of smoking, drinking, and usage of antiplatelet drugs. Hypertension was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or a history of hypertension as reported by the subject. Diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dL (7.0 mmol/L), a random blood glucose level is ≥200 mg/dL (11.1 mmol/L), or a reported treatment for diabetes mellitus. A current drinker was defined as a person who consumed alcohol more than 1 day per week. A current smoker was defined as a person who smoked every day.

2.3. MRI scanning parameters

Cranial MRI was performed with a Signa HD 1.5-Tesla MRI scanner (GE, Fairfield, CT). The image acquisition parameters were the same as our previous study.[12]

2.4. Image analysis

CMBs were defined as small-foci signal loss with a diameter of 2 to 10 mm on T2*-weighted angiography images. CMBs were differentiated from vascular flow voids, calcifications or non-hemorrhagic iron deposits in the basal ganglia. Both calcium and iron deposits are usually found bilaterally in the basal ganglia, although calcification can also occur in the choroid plexus, pineal gland, and lobar locations. Computed tomography can facilitate the identification of suspected calcification. Vascular flow voids can be distinguished from CMBs by their location, equal visibility on T2*-weighted GRE sequence, and linear structure when examined over contiguous slices.[3] The location of CMBs was assessed by the Microbleed Anatomical Rating Scale.[13] CMBs were classified into deep, lobar, and infratentorial categories according to location. Lobar regions included cortical and subcortical regions. Deep regions included the basal ganglia, internal capsule, corpus callosum, external capsule, thalamus and deep and periventricular white matter. Infratentorial regions included the brainstem and cerebellum.

White matter hyperintensities on MRI were classified as peri-ventricular hyperintensities (PVH) or deep white-matter hyperintensities (DWMH). The severity of PVH and DWMH was visually rated on T2-fluid-attenuated inversion recovery (FLAIR) images using Fazekas's classification (ranging from 0 to 3) .[14]

Lacunar infarcts were defined as small cavities with diameters of 3 to 15 mm and signal intensities comparable to cerebro-spinal fluid on T2-weighted imaging. They consist of focal cerebro-spinal fluid filled cavities, often surrounded by a hyperintense rim on T2- FLAIR sequence. The number of lacunar infarcts was recorded for each subject, and the severity of the lacunar infarcts was classified into 4 grades (0 = absent, 1 = with 1 lacunar infarct lesion, 2 = lesions ranging from 2 to 4, 3 = more than 4 lesions).

The MRI images were independently evaluated by 2 associate chief physicians who were blind to the patients' clinical data.

2.5. Statistical analysis

Data are expressed as means ± standard deviations or proportions (%). We applied the independent samples t-test and χ^2 test, where appropriate, to compare clinical characteristics between patients with and without CMBs. Logistic regression analysis was performed to examine the risk factors of CMBs. Variables which showed a significant difference in univariate analysis were included in the logistic regression as independent variables. The presence, number, and severity of lacunar infarcts were separately included in the logistic regression analysis as model 1, 2, and 3, with other independent variables including hypertension, PVH severity, and DWMH severity. The percentage of patients with different types of CMBs in different groups of lacunar infarcts severity was compared by χ^2 test. Differences were considered significant when $P < .05$. All of the statistical analyses were performed with SPSS version 16.0 (SPSS, Chicago, IL).

3. Results

3.1. Clinical characteristics and risk factors of CMBs

Of the 166 patients, CMBs were present in 77 (46.4%) patients. The clinical characteristics of patients with and without CMBs are shown in Table 1. The factors associated with CMBs were age ($P = .041$), hypertension ($P < .001$), severity of PVH ($P = .001$), severity of DWMH ($P = .001$) and severity of lacunar infarcts ($P = .001$). Lacunar infarcts were more frequently observed in patients with CMBs (64/77, 83.1%) than in those without CMBs (53/89, 59.5%; $P = .001$). Logistic regression analysis of the risk factors for CMBs showed that the presence of lacunar infarcts (odds ratios (OR) 2.14, 95% confidence interval (CI) 1.02–4.48) and hypertension (OR, 5.76; 95% CI, 2.01–16.55) in model 1, number of lacunar infarcts (OR 1.17, 95% CI 1.02–1.36) and hypertension (OR, 5.34; 95% CI, 1.88–15.19) in model 2, and severity of lacunar infarcts (OR 1.61, 95% CI 1.07–2.42) and hypertension (OR, 5.38; 95% CI, 1.89–15.34) in model 3 were significantly associated with CMBs (Table 2).

3.2. Location of CMBs and risk factors of CMBs in different location

A total of 393 CMBs were detected in 77 patients, with 48.1% located in cortical region, 13.7% located in infratentorial region, and 34.6% located in deep region. The number of subjects with CMBs and the number of CMBs in different locations are shown in Table 3.

Logistic regression analysis of the risk factors for CMBs distribution showed that the number (OR 1.18, 95% CI 1.03–1.36) and severity of lacunar infarcts (OR 1.71, 95% CI 1.11–2.63) were independent risk factors for deep CMBs. Hypertension was a risk factors for both deep and lobar CMBs ($P < .05$), but not for infratentorial CMBs in all models (Table 4).

3.3. Relationship between CMBs and severity of lacunar infarcts

The relationship between the location of CMBs and the severity of lacunar infarcts is showed in Figure 1. The proportion of the total CMBs increased as the severity of lacunar infarcts increased; CMBs were found in 69.2% (9/13) of patients with grade 3 lacunar infarcts, compared with 56.7% (17/30), 51.4% (37/72), and 27.5% (14/51) of patients with grade 2, grade 1 and without

Table 1

Clinical characteristic of subjects with and without CMBs.

Variable	CMBs		P value
	Absent (n = 89)	Present (n = 77)	
Sex (male/female)	86/3	75/2	.771
Age (years)	81.46 ± 8.47	83.94 ± 7.39	.048
Age n (%)			.041
<79	30 (33.7)	13 (16.9)	
80-89	45 (50.6)	46 (59.7)	
>90	14 (15.7)	18 (23.4)	
Current smoker n (%)	51 (57.3)	44 (57.1)	.983
Current drinker n (%)	27 (30.3)	24 (31.2)	.908
Type 2 diabetes n (%)	37 (41.6)	31 (40.3)	.864
Glucose, mmol/L	5.34 ± 1.07	5.50 ± 1.06	.334
Hypertension n (%)	61 (68.5)	72 (93.5)	< .001
SBP, mm Hg	124.85 ± 14.82	126.43 ± 21.75	.582
DBP, mm Hg	68.18 ± 7.62	67.96 ± 8.89	.865
Presence of lacunar infarcts n (%)	53 (59.5)	64 (83.1)	.001
Number of lacunar infarcts	1.64 ± 2.19	3.04 ± 3.09	.001
Severity of lacunar infarcts			.007
Grade 1	35 (39.3)	37 (48.1)	
Grade 2	13 (14.6)	17 (22.1)	
Grade 3	4 (4.5)	9 (11.7)	
Severity of PVH			.001
Grade 1	40 (44.9)	22 (28.6)	
Grade 2	14 (15.7)	27 (35.1)	
Grade 3	5 (5.6)	13 (16.9)	
Severity of DWMH			.001
Grade 1	47 (60.3)	31 (39.7)	
Grade 2	5 (20.8)	19 (79.2)	
Grade 3	3 (30.0)	7 (70.0)	
Usage of Ant platelet drugs n (%)	71 (53.4)	62 (46.6)	.905

CMBs = cerebral microbleeds, DBP = diastolic blood pressure, DWMH = deep white matter hyperintensity, PVH = periventricular hyperintensity, SBP = systolic blood pressure.
* P < .05 vs subjects without CMBs.

lacunar infarcts, respectively ($P = .007$, χ^2 test). A similar pattern was observed in the association between deep CMBs and the severity of lacunar infarcts. Deep CMBs were found in 53.8% (7/13) of patients with grade 3 lacunar infarcts, compared with 46.7% (14/30), 29.2% (21/72), and 13.7% (7/51) of patients with grade 2, grade 1 and without lacunar infarcts ($P = .003$, χ^2 test). There was no significant relationship between lobar CMBs, infratentorial CMBs, and the severity of lacunar infarcts.

4. Discussion

In our study, CMBs could be detected in approximately half of the patients with ischemic stroke or TIA. The frequency was higher than in previous studies where microbleeds presented in about 5% of healthy adults, 34% of patients with ischemic stroke, and 60% of people with primary intracerebral hemor-rhage.[15] We observed that CMBs were present in 46.4% of patients with ischemic stroke or TIA. The prevalence of CMBs also increased with age. CMBs were reported to range from 6.5% in patients under 50 years to 35.7% in patients more than 80 years of age in the Rotterdam scan study.[11] From our findings, CMBs were found in 64 of 123 (52.0%) patients older than 80 years, higher than that in the above report.

In our study, nearly half of CMBs were present in the cortical region. Among 189 cortical lesions, about 70% were located in the frontal and temporal lobes. Almost one-third of CMBs occurred in the deep region including the thalamus, basal ganglia, internal capsule, external capsule, corpus callosum, and deep white matter. CMBs in the deep region were predominantly observed in the thalamus, and then in the basal ganglia. Although CMBs could be detected in almost any part of the brain parenchyma, they were more frequently seen in the frontal lobe,

Table 2

Logistic regressions of risk factors to predict CMBs.

Variable	Model 1	Model 2	Model 3
Hypertension	5.76 (2.01–16.55)*	5.34 (1.88–15.19)*	5.38 (1.89–15.34)*
Severity of PVH	1.50 (0.87–2.60)	1.50 (0.87–2.58)	1.49 (0.86–2.58)
Severity of DWMH	1.26 (0.69–2.28)*	1.16 (0.64–2.12)	1.20 (0.66–2.18)
Presence of lacuar infarcts	2.14 (1.02–4.48)*		
Number of lacunar infarcts		1.17 (1.02–1.36)*	
Severity of lacunar infarcts			1.61 (1.07–2.42)*

CMBs = cerebral microbleeds, DWMH = deep white matter hyperintensity, PVH = periventricular hyperintensity.
* P < .05 vs subjects without CMBs.

Table 3

Location of CMBs using Microbleed Anatomical Rating Scale (MARS).

Region	Number of subjects with CMBs	Number of CMBs lesions	Percentage of total lesions
Cortical	48	189	48.09
Frontal lobe	23	45	11.45
Parietal lobe	15	34	8.65
Occipital lobe	15	28	7.12
Temporal lobe	28	82	20.87
Infratentorial	27	68	17.30
Cerebellum	20	35	8.91
Brain stem	13	33	8.39
Deep	49	136	34.61
Basal ganglia	15	28	7.12
Thalamus	23	60	15.26
Internal capsule	4	10	2.54
External capsule	4	4	1.01
Corpus callosum	1	1	0.25
DPWM	23	33	8.39
Total	77	393	100

CMBs = cerebral microbleeds, DPWM = deep and periventricular white matter.

Table 4

Logistic regressions of risk factors to predict CMBs in different distribution.

	Lobal CMBs	Infratentorial CMBs	Deep CMBs
Model 1			
Hypertension	7.29 (1.62–32.93)[*]	1.55 (0.41–5.89)	6.96 (1.53–31.74)[*]
Severity of PVH	1.69 (0.97–2.95)	1.66 (0.83–3.35)	1.10 (0.63–1.94)
Severity of DWMH	1.13 (0.62–2.07)	1.57 (0.74–3.31)	2.05 (1.07–3.91)[*]
Presence of lacuar infarcts	1.06 (0.47–2.38)	2.15 (0.72–6.45)	2.21 (0.93–5.27)
Model 2			
Hypertension	7.40 (1.64–33.32)[*]	1.65 (0.43–6.28)	6.08 (1.35–27.38)[*]
Severity of PVH	1.69 (0.97–2.94)	1.67 (0.85–3.30)	1.15 (0.66–2.01)
Severity of DWMH	1.14 (0.62–2.11)	1.60 (0.76–3.35)	1.83 (0.96–3.52)
Number of lacunar infarcts	0.99 (0.88–1.14)	1.04 (0.89–1.20)	1.18 (1.03–1.36)[*]
Model 3			
Hypertension	7.34 (1.63–33.08)[*]	1.59 (0.41–6.07)	6.17 (1.37–27.90)[*]
Severity of PVH	1.69 (0.97–2.95)	1.67 (0.84–3.29)	1.12 (0.64–1.97)
Severity of DWMH	1.13 (0.62–2.08)	1.58 (0.76–3.31)	1.91 (0.99–3.66)
Severity of lacunar infarcts	1.01 (0.67–1.53)	1.20 (0.74–1.94)	1.71 (1.11–2.63)[*]

CMBs = cerebral microbleeds, DWMH = deep white matter hyperintensity, PVH = periventricular hyperintensity.
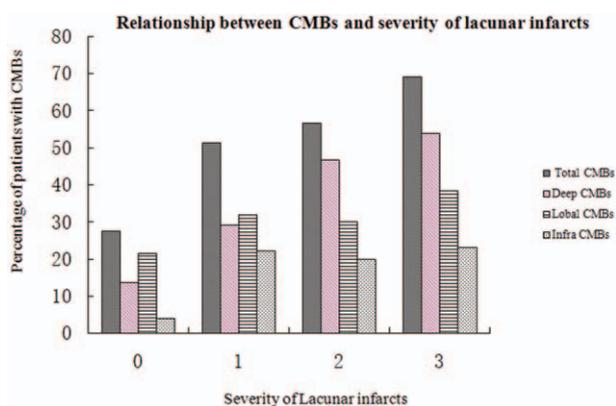
[*] $P < .05$ vs subjects without CMBs.

Figure 1. The relationship between the location of cerebral microbleeds (CMBs) and the severity of lacunar infarcts. The bars showed the percentage of patients with the total and different types of CMBs in differing lacunar infarcts severities. The percentage of total and deep CMBs increased with an increase in the lacunar infarcts severity ($P = .007$; $P = .003$, respectively). CMBs = cerebral microbleeds.

temporal lobe, and thalamus. Our results coincide with those of a previous study that had a 43.95% cortical and 19.77% thalamic distribution of CMBs.[16]

Age and hypertension are wildly accepted as risk factors for CMBs.[11,15,17] The association between the severity of hypertension and CMBs was observed in northeast Chinese, without a preceding large-area stroke.[16] In previous studies, various ambulatory hypertension indices were reported to be associated with deep but not lobar CMBs.[18] Liu et al[19] found that blood pressure variability independently predicted CMBs progression in the deep and infratentorial regions. We confirmed that the relationship between hypertension and CMBs was independent of age, sex, and white matter lesions. Furthermore, we found that hypertension predicted cortical and deep CMBs but not infratentorial CMBs after stratification by CMBs location. Smoking, alcohol, and diabetes, which are common risk factors for vascular disease, were included in the analysis of risk factors for CMBs but were not related to the presence of CMBs. Our result was consistent with those of previous studies,[6,16,20,21] possibly because smoking and alcohol consumption and diabetes are more closely related to macroangiopathy than small vessel disease.

Our study agrees with a previous study that reported a significant correlation between the number of infarcts and the number of CMBs in patients with lacunar stroke.[8,9] We observed that both the presence and severity of lacunar infarcts predicted CMBs. Moreover, the proportion of CMBs increased as the severity of lacunar infarcts increased. Although the severity of PVH and DWMH were risk factors for CMBs in univariate analysis, they did not show any significant association with CMBs in multivariate regression analysis.

The Rotterdam Scan Study showed that deep or infratentorial microbleeds, but not lobar microbleeds, were associated with lacunar infarcts.[11] We also found a significant association between lacunar infarcts and the presence of deep CMBs in patients with ischemic stroke or TIA, but we did not observe such a relationship between lacunar infarcts and infratentorial CMBs. The frequency of deep CMBs significantly increased with the severity of lacunar infarcts. Since, CMBs in the deep white matter were associated with hypertensive vasculopathy. The association between deep CMBs and lacunar infarcts indicates that they are the consequence of hypertension.

Our study has several limitations. First, it was an observational study. Moreover, we could not exclude the relationship between lacunar infarcts and the progression of CMBs. In addition, the sensitivity of CMBs detection depends on MRI sequence and characteristics. We detected CMBs on T2*-weighted angiography with a 1.5-T magnetic field strength. To our knowledge, a 3-Tesla or higher field strength.[22,23] and susceptibility-weighted imaging[24] seem to improve the detection rate of CMBs. Finally, our sample size was rather small. Larger series are needed to confirm our findings.

The present study demonstrated the relationship between CMBs and lacunar infarcts. Further statistical analysis suggested that deep CMBs, rather than lobar CMBs and infratentorial CMBs, are associated with lacunar infarcts.

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Author contributions

Conceptualization: Zhongbao Gao, Zhenfu Wang.
Data curation: Zhongbao Gao, Yongzhi Zhai, Xingli Zhao, Wei Wang, Ruozhuo Liu.
Formal analysis: Zhongbao Gao, Xingli Zhao, Wei Wang, Xiaodan Wang.
Funding acquisition: Zhongbao Gao, Ruozhuo Liu.
Investigation: Zhongbao Gao, Yongzhi Zhai, Zhenfu Wang, Xiaodan Wang.
Methodology: Zhongbao Gao, Yongzhi Zhai, Zhenfu Wang, Xiaodan Wang.
Project administration: Zhongbao Gao, Weiping Wu, Zhenfu Wang.
Resources: Zhongbao Gao, Yongzhi Zhai, Xingli Zhao, Weiping Wu, Ruozhuo Liu.
Software: Zhongbao Gao, Yongzhi Zhai, Xingli Zhao, Wei Wang, Ruozhuo Liu.
Supervision: Weiping Wu, Zhenfu Wang, Xiaodan Wang.
Validation: Wei Wang, Weiping Wu, Zhenfu Wang, Xiaodan Wang.
Visualization: Zhongbao Gao, Zhenfu Wang, Xiaodan Wang.
Writing – original draft: Zhongbao Gao, Yongzhi Zhai.
Writing – review & editing: Zhongbao Gao, Xiaodan Wang.

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