JoS JOURNAL OF STROKE

Journal of Stroke 2013;15(3):153-163
http://dx.doi.org/10.5853/jos.2013.15.3.153

Review

Cerebral Microbleeds: Their Associated Factors, Radiologic Findings, and Clinical Implications

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Cerebral microbleeds (CMBs) are tiny, round dark-signal lesions that are most often detected on gradient-echo MR images. CMBs consist of extravasations of blood components through fragile microvascular walls characterized by lipohyalinosis and surrounding macrophages. The prevalence of CMBs in elderly subjects with no history of cerebrovascular disease is around 5%, but is much higher in patients with ischemic or hemorrhagic stroke. Development of CMBs is closely related to various vascular risk factors; in particular, lobar CMBs are thought to be associated with cerebral amyloid angiopathy. The presence of CMBs has been hypothesized to reflect cerebral-hemorrhage-prone status in patients with hypertension or amyloid microangiopathy. Stroke survivors with CMBs have been consistently found to have an elevated risk of subsequent hemorrhagic stroke or an antithrombotic-related hemorrhagic complication, although studies have failed to establish a link between CMBs and hemorrhagic transformation after thrombolytic treatment. A large prospective study is required to clarify the clinical significance of CMBs and their utility in a decision-making index.

Keywords Cerebral microbleed; Ischemic stroke; Intracerebral hemorrhage; Antithrombotics; Gradient-echo MRI

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Received: July 28, 2013
Revised: August 29, 2013
Accepted: September 9, 2013

The authors have no financial conflicts of interest.

Introduction

The term cerebral microbleed (CMB) refers to small, round dark-signal lesions detected by T2*-weighted or gradient-echo (GRE) magnetic resonance imaging (MRI).[1] CMBs were introduced to stroke physicians in the late 1990s and early 2000s after development of MRI techniques sensitive to paramagnetic effects.[2] The clinical significance of CMBs has been actively investigated, especially in the stroke field and more recently in studies on cognitive impairment and aging.[3] Histological investigation has shown that CMBs are tiny foci containing hemosiderin-laden macrophages and abnormal microvessels showing fibrohyalinosis.[4,5] Clinical cases with frank symptoms caused by CMBs are uncommon. Because CMBs are manifestations of focal extravascular leakage of blood components, however, investigators have suggested that accumulation of CMBs reflects a bleeding-prone status in individuals with an elevated risk of cerebral hemorrhage. Clinical studies have found strong associations between CMBs and chronic hypertension and low cholesterol levels,[6,7] and between the proximity and volume of CMBs and those of subsequent intracerebral hemorrhage (ICH).[8,9] Longitudinal studies have found that CMBs are linked to subsequent hemorrhagic stroke in stroke survivors,[10] and suggested that CMBs are related to antithrombotic-related hemorrhage.[11,12] In this review, we discuss fundamental findings of CMBs, and the clinical implications of these observations for the field of cerebrovascular disease.

Visualization and detection of cerebral microbleeds

GRE sequences are more sensitive to susceptibility effects than are classical MRI sequences. Unlike classical T2-weighted imaging or echo-planar sequences, GRE sequences maximize the paramagnetic effects of blood components such as hemosiderin, deoxyhemoglobin, and ferritin.[2,13] Due to the dephasing of MRI signals, GRE sequences tend to exaggerate lesion sizes. Therefore, sub-millimeter CMBs appear as signal-loss lesions of several millimeters, a phenomenon referred to as the blooming effect.

Susceptibility-weighted imaging (SWI) is a MRI sequence that maximizes sensitivity to magnetic susceptibility effects.[14,15] SWI requires more time than does GRE, and also requires post-processing, but because SWI accentuates the magnetic properties of tissues, it enables visualization of areas such as CMBs containing deoxygenated blood substances.[16] SWI permits visualization of a greater number of CMBs than can be seen with conventional GRE sequences, but the clinical implications of this increased sensitivity are not yet fully understood (Figure 1).[17]

Since CMBs are primarily a radiologic concept, their sizes and shapes are dependent upon the parameters of the GRE sequence. Visualization of CMBs is thought to be influenced by pulse sequence, sequence parameters, spatial resolution, magnetic field strength, and post-processing of images.[1] Thus, lesions due to old parenchymal hemorrhage, cortical or deep-seated mineralizations, or vascular malformations potentially all can be misinterpreted as CMBs. Small cortical vessels, partial volume effects of the cerebellar cortex, and cavernous hemangiomas also should be considered (Figure 2).[21] Moreover, multifocal bleeding spots caused by diffuse axonal injury are virtually impossible to distinguish from cortico-subcortical CMBs.

Comparison of magnetic field strength in detection of CMBs revealed 0.5 more microbleeds on average could be observed using a 3.0 Tesla MRI compared to a 1.5 Tesla unit (2.1 in 3.0 T and 1.6 in 1.5 T).[18] No universal standard MR parameters exist for the detection of CMBs, and in addition, the definition of CMB size also varies. In published reports, the lower limit of CMB size is usually ≤ 2 mm, and the upper limit is usually between 5 and 10 mm.[19] Greenberg et al. reported that the size distribution of microbleeds and macrobleeds is bimodal, and proposed that the most appropriate cut-off point between them is 5.7 mm.[20] Those researchers suggested elsewhere that an upper size limitation is impractical, and that instead, a more desirable approach is to carefully exclude CMB-mimicking lesions such as those described above.[1] Other investigators have proposed a specified rating scale for CMBs, the Microbleed Anatomical Rating Scale.[21] In our view, setting an appropriate upper-size limitation, and determination of intra- and inter-rater

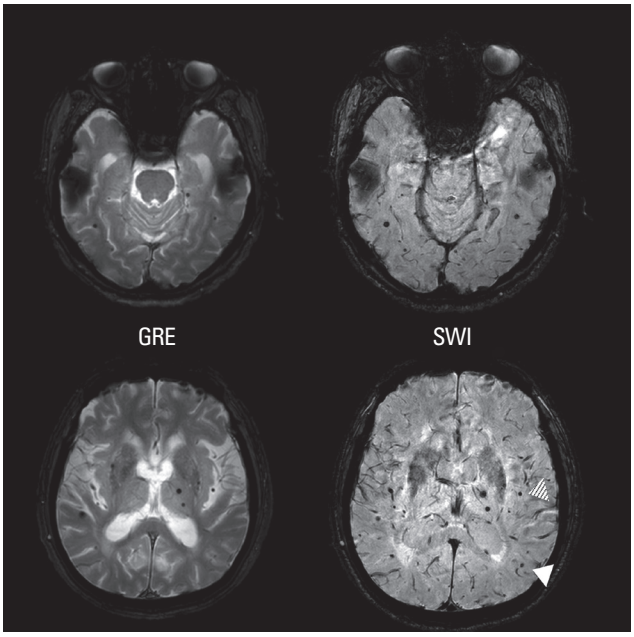

Figure 1. Cerebral microbleeds (CMBs) visualized on gradient-echo (GRE) images and susceptibility-weighted images (SWI). A lobar CMB on a SWI image (white arrow) is only faintly visible on the corresponding GRE image. Vessels located in the subarachnoid space could be mistakenly identified as CMBs on SWI sequence (hatched arrows).

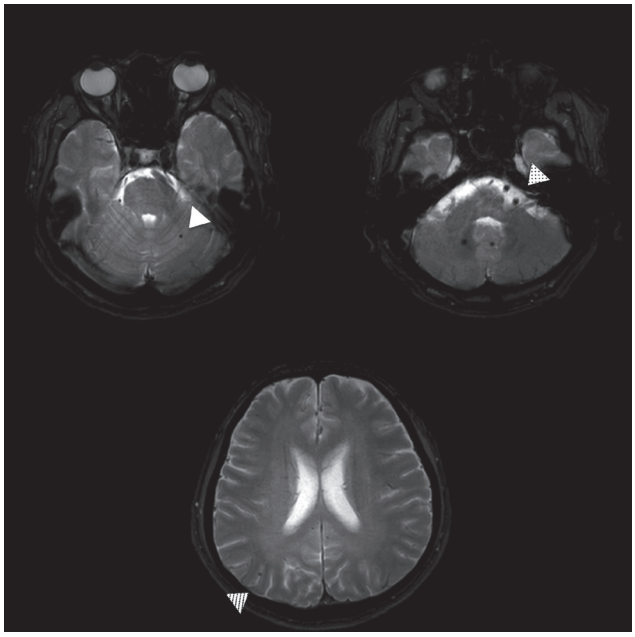

Figure 2. Cerebellar microbleeds (CMBs; white arrow). Two vertebral arteries in the subarachnoid space look similar to microbleeds (dotted arrow). One vessel signal located inside of a sulcus could be mistakenly interpreted as a CMB (hatched arrow).

http://dx.doi.org/10.5853/jos.2013.15.3.153

agreement values, are necessary for clinical and radiologic research studies.

Pathology of cerebral microbleeds

Pathologic-radiologic correlation studies have revealed that CMBs are focal accumulations of hemosiderin adjacent to abnormal blood vessels demonstrating fibrolipohyalinosis or amyloid microangiopathy.[4,5] CMBs usually develop adjacent to capillaries, small arteries, or arterioles; hemosiderin-laden macrophages are usually present.[22] A recent pathological investigation of CMBs in patients with cerebral amyloid angiopathy demonstrated extravasation of blood and hemosiderin through vulnerable vascular walls, with β-amyloid pigmentation and surrounding inflammation.[23] These findings suggest that CMBs are the radiologic correlates of extravasation of blood components through injured or fragile vascular walls, or of frank small hemorrhage spots. In the context of cerebral amyloid angiopathy, Greenberg et al. suggested that increased vascular wall thickness was indicative of microbleeds.[20]

Because blooming artifact on GRE images exaggerates the size of CMBs, it has been proposed that the actual size of hemosiderin deposition is too small to cause apparent neurological deficit.[22] Selected cases, however, have suggested that CMBs can cause neurological symptoms and signs.[24,25]

Prevalence and associated factors for cerebral microbleeds

Cerebral microbleeds in healthy subjects

In subjects without a history of cerebrovascular disease, the prevalence of CMBs was reported to be between 3-7%.[26-33] Significant associations have been consistently reported between CMBs and advanced age, as well as hypertension.[33] In contrast, association between CMBs and diabetes has been inconsistent across published reports.[19,34,35] The Rotterdam Scan Study described CMBs in 1,062 older subjects.[39] In a group of patients with mean age 69.6 years and a hypertension prevalence of 71.9%, CMBs were detected in 17.8% of patients aged 60-69, in 31.3% of patients aged 70-79, and in 38.3% of patients aged 80-97. The prevalence of multiple CMBs was also found to increase significantly with age.[37] A single-hospital-based cross-sectional study performed in Japan found no deep-seated CMBs in subject younger than 40 years old.[38] The Rotterdam Scan Study also noted a strong association of very low serum cholesterol levels (< 4.42 mmol/L versus higher values) with the presence of strictly lobar microbleeds,[39] an observation consistent with our earlier findings.[7]

Cerebral microbleeds in ischemic stroke patients

The reported prevalence of CMBs in ischemic stroke patients varies significantly (35%-71%; Table 1).[27,38,40-43] This variability may be due to the heterogeneity of ischemic stroke *per se*, or to differences in recruited populations, rating strategies, and MRI parameters. Two studies investigating CMB frequency in different ischemic stroke subtypes found that CMBs were less frequent in cardioembolic stroke than in atherothrombotic stroke or lacunar stroke.[28,44] Accumulation of sublethal ischemic injuries in brain parenchyma is thought to differ in atherothrombotic stroke and cardioembolic stroke,[45] suggesting that the relationship of CMBs and stroke subtype in turn may reflect a different degree of fragility of vascular walls. A recent study found that the absolute number of CMBs, as well as variability indices of blood pressure (including coefficient of variance and successive variation), were elevated in cases of ischemic stroke with CMBs.[46]

Another analysis of patients with ischemic stroke reported that serum uric acid level was associated in a dose-dependent manner with the presence of CMBs, but only in hypertensive patients.[47] Complex interactions have been observed between chronic medical conditions and individual serologic markers in development of CMBs, such as in ischemic stroke patients with chronic kidney disease. Proteinuria and impaired kidney function has been linked to with small vessel disease in the brain and to CMBs.[48-51] We further analyzed this issue, and found that chronic kidney disease is independently associated with cerebral microbleeds in patients without diabetes, but not in patients with diabetes.[52]

Cerebral microbleeds in hemorrhagic stroke patients

The frequency of CMBs in hemorrhagic stroke patients has been consistently higher than that that in ischemic stroke patients, reaching 50% to 80%.[4,8,53-55] (Table 2; Figure 3) The detection rate of CMBs is higher in Asian populations, which may reflect a higher prevalence of the hemorrhagic stroke subtype in this ethnic group.[56] CMBs also have been reported to be associated with hematoma volume, regardless of perihematomal edema volume.[9] Patients with cerebral amyloid angiopathy have a higher CMB detection rate, with a preference for a lobar location,[57,58] and the presence of the APOE e4 allele also has been reported to favor a lobar location (Figure 4).[39,59]

Longitudinal changes in the number of cerebral microbleeds

The appearance and disappearance of CMBs over time have not been highlighted sufficiently. In an analysis of 237 acute ischemic stroke patients who underwent follow-up imaging,

Table 1. Prevalence of cerebral microbleeds in ischemic stroke patients

First author (year)	Patient characteristics	Cases number	Average age	Prevalence (%)	Associated findings
Kinoshita (2000)[27]	Multiple lacunar infarcts with hypertension	68	68.8 [55-88]	65	5% in non-stroke controls
Kato (2002)[28]	Ischemic stroke patients with variable time-point of MR imaging	113			Correlation between number of microbleeds and severity of white matter hyperintensities
	Atherothrombotic stroke	24	74±10	21	
	Cardioembolic stroke	23	77±6	30	
	Lacunar stroke	66	74±9	62	
Tsushima (2003)[38]	History of ischemic stroke	232	NR	18	71% in hemorrhagic stroke patients and 3.7% in non-stroke controls
Hanyu (2003)[30]	Multiple lacunar stroke	51	75±7	51	Higher cerebral microbleed (CMB) prevalence in so-called Binswanger disease
Fan (2003)[10]	Consecutive acute ischemic stroke within 7 days after onset	121	68±11	36	CMBs as a risk factor of subsequent hemorrhagic stroke in AIS survivors
Lee (2004)[40]	Consecutive ischemic stroke patients [admitted 2000-2001]	113	65±9	65	CMBs distribution is similar to apparent regional predilection of intracerebral hemorrhage (ICH)
Lee (2004)[6]	Consecutive acute ischemic stroke patients [admitted 1998-1999]	144	65±9	35	Regional association between CMBs and ICH
Naka (2004)[44]	First ever ischemic stroke patients		69±13		CMBs associated with recurrent stroke and leukoaraiosis
	Atherothrombotic stroke	22		23	
	Cardioembolic stroke	13		0	
	Lacunar stroke	31		23	
Imaizumi (2004)[43]	Consecutive lacunar infarction patients	138	66±9	51	Multiple CMBs (≥3) associated with recurrent events
Schoenwille (2005)[81]	Consecutive lacunar infarction patients, within 7 days after onset	68	NR	46	
Werring (2005)[82]	Consecutive ischemic stroke patients	86	62±16	23	
	Consecutive TIA patients	43	67±9	2	
Boulanger (2006)[69]	Ischemic stroke or TIA patients	236		19	CMBs associated with subsequent fatal or disabling stroke
Ovbiagele (2006)[83]	Consecutive ischemic stroke or TIA patients	164	78 (MB+), 73 (MB-)	35	
	Large vessel disease	40		18	
	Small vessel disease	44		61	
	Cardioembolism	39		26	
Wardlaw (2006)[84]	Patients with mild stroke (partial anterior, lacunar and posterior circulation syndrome)	241	66 [19-89]	20	CMBs associated with the clinicoradiologic syndrome of lacunar ischemic stroke
Fiehler (2007)[75]	Acute ischemic stroke patients within 6 h after onset	570	69 [IQR, 59 and 77]	15	No incremental symptomatic ICH after thrombolysis in presence of CMBs
Lee (2008)[74]	Acute ischemic stroke patients with large artery atherosclerosis or cardioembolic stroke	377	66±12	29	No incremental hemorrhagic transformation in presence of CMBs
Seo (2008)[85]	Acute ischemic stroke or TIA patients	255	64±12	22	CMBs associated with pulse wave velocity
Cho (2009)[51]	Consecutive acute ischemic stroke patients	152	67±12	30	MBs associated with impaired kidney function
Jeon (2009)[60]	Consecutive acute ischemic stroke patients within 24 hr after onset	237	64±13	32	New CMBs after acute ischemic stroke
Fiehler (2009)[86]	100 consecutive acute ischemic stroke patients who received thrombolytic treatment	100	62±13	21	Presence of CMB being not associated with post-thrombolytic parenchymal hematoma
Staals (2009)[87]	Lacunar infarct patients	123	65±12	29	High 24-h blood pressure level is associated with the presence of CMBs
Ovbiagele (2010)[48]	Consecutive patients with ischemic stroke or TIA	236	74 (range, 23-100)	31	Proteinuria associated with frequency and number of CMBs
Ryu (2012)[52]	Consecutive ischemic stroke patients	909	67±11 (+) 64±12 (-)	28	Chronic kidney disease associated with non-diabetic patients but not with diabetic patients
Fluri (2012)[88]	Consecutive TIA cases	176	69±13	15	Presence of CMBs in TIA patients associated with subsequent ischemic stroke within 3 months

AIS, acute ischemic stroke; TIA, transient ischemic attack; MB, microbleeds; IQR, interquartile range; NR, not reported.

13% had new CMBs (56 microbleeds in total) in the subsequent GRE images taken on average after 4 days.[60] Long-term follow-up also revealed that 23% of cases demonstrated new CMBs on GRE imaging performed on average over 5.6 years.[61] Development of new CMBs in this study was associated with high blood pressure and the presence of CMBs on baseline imaging. An additional follow-up study published in 2012 reported that the number of CMBs was increased in 54% of cases after 2.5 years.[62] The annual change of CMBs significantly correlated with the number of CMBs on the baseline study. Another inter-

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Table 2. Prevalence of cerebral microbleeds in hemorrhagic stroke patients

First author (year)	Patients characteristics	Case number	Age	Prevalence (%)	Associated findings
Tanaka (1999)[4]	Intracerebral hemorrhage (ICH) patients	30	60 [43-77]	57	Providing pathological correlation data
Roob (2000)[89]	Consecutive primary ICH patients	109	65 [22-91]	54	Cerebral microbleeds (CMBs) associated with white matter hyperintensities and lacunar infarctions
Kinoshita (2000)[27]	ICH proved by computed tomography (CT) within 2 days after onset	130	64 [24-86]	71	5% in non-stroke controls
Kato (2002)[28]	Hemorrhagic stroke patients with variable time-point of magnetic resonance imaging (MRI)	35	72±11	71	Correlation between number of microbleeds and number of ICH
Tsushima (2003)[38]	History of hemorrhagic stroke	69	63±10	71	Increased distribution of lobar CMBs in lobar ICH patients, compared to patients with deep ICH
Jeong (2004)[53]	Consecutive primary ICH patients	107	62±13	70	CMBs associated with white matter hyperintensities and lacunar infarcts
Lee (2004)[6]	Consecutive ICH patients with hypertension [admitted, 2000-2001]	51	65±9	73	CMB distribution similar to apparent regional predilection of ICH
Lee (2004)[8]	Consecutive acute hemorrhagic stroke patients [admitted 1998-1999]	83	66±11	80	Regional association between CMBs and ICH
Greenberg (2004)[54]	Consecutive primary lobar ICH patients	94	≥55	59	New CMBs in follow-up imaging associated with recurrent ICH
Naka (2004)[44]	First-ever hemorrhagic stroke patients	36	69±13	47	CMBs associated with recurrent stroke and leukoaraiosis
Imaizumi (2004)[90]	Consecutive deep ICH patients	199	66±11	77	Multiple CMBs (≥ 3) associated with recurrent events
Lee (2005)[67]	Consecutive primary ICH patients [admitted 2002-2003]	70	70±10	97	CMBs in basal ganglia and thalamus have higher predictive value for ICH
Jeon (2007)[65]	Primary ICH patients with follow-up	63	59±9	68	Number of CMBs associated with recurrent ICH
Lim (2009)[91]	Primary hemorrhagic stroke cases	234	61±12	80	
Nishikawa (2009)[92]	Spontaneous ICH cases	166	69±12 (+) 64±11 (-)	55	
Haussen (2012)[93]	Consecutive spontaneous ICH patients with brain MRI within 30 days of presentation	176	68±15	52	Pre-ICH statin use associated with the presence of CMB

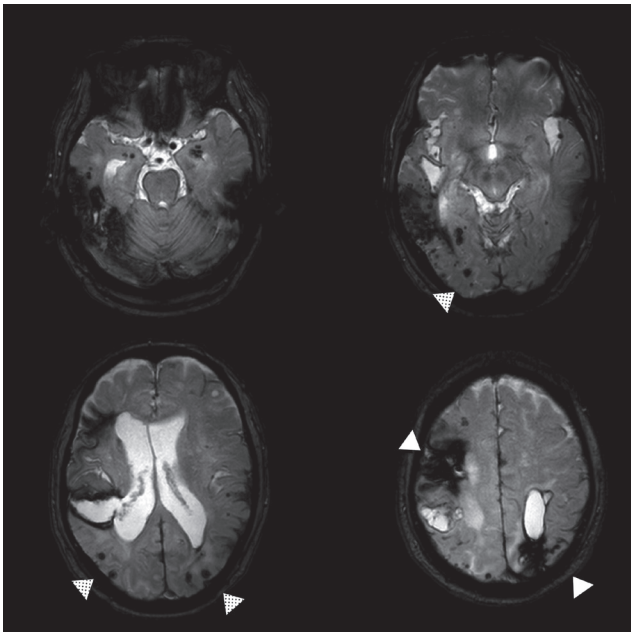

Figure 3. Gradient-echo (GRE) images from a case of multiple lobar hemorrhage (white arrow). Multiple lobar cerebellar microbleeds (CMBs) are visible (dotted arrows).

esting finding in that report was that in 15% of patients, CMBs disappeared on the follow-up GREs. Follow-up analyses of CMBs must be interpreted with caution, however, since spatial registration of baseline and follow-up images has not been performed in any published studies. Use of rigorous rating criteria[21] is another important factor necessary for detailed evaluation of the natural history of CMBs, including their development and disappearance.

Clinical implications of cerebral microbleeds

Further understanding of the characteristics of CMBs has generated interest in using detection of CMBs to enable hemorrhagic stroke risk stratification. A number of reports have described the hemorrhagic tendency of CMBs.[24,63,64] A hemorrhagic transformation after multiple embolic infarctions occurred only in the site of the known CMB.[63] A Hong Kong study followed 121 acute ischemic stroke patients, and observed that stroke survivors with CMBs on their initial MRI scans had a higher risk of subsequent hemorrhagic stroke.[10] Hemorrhage counts in initial scans also were found to be pro-

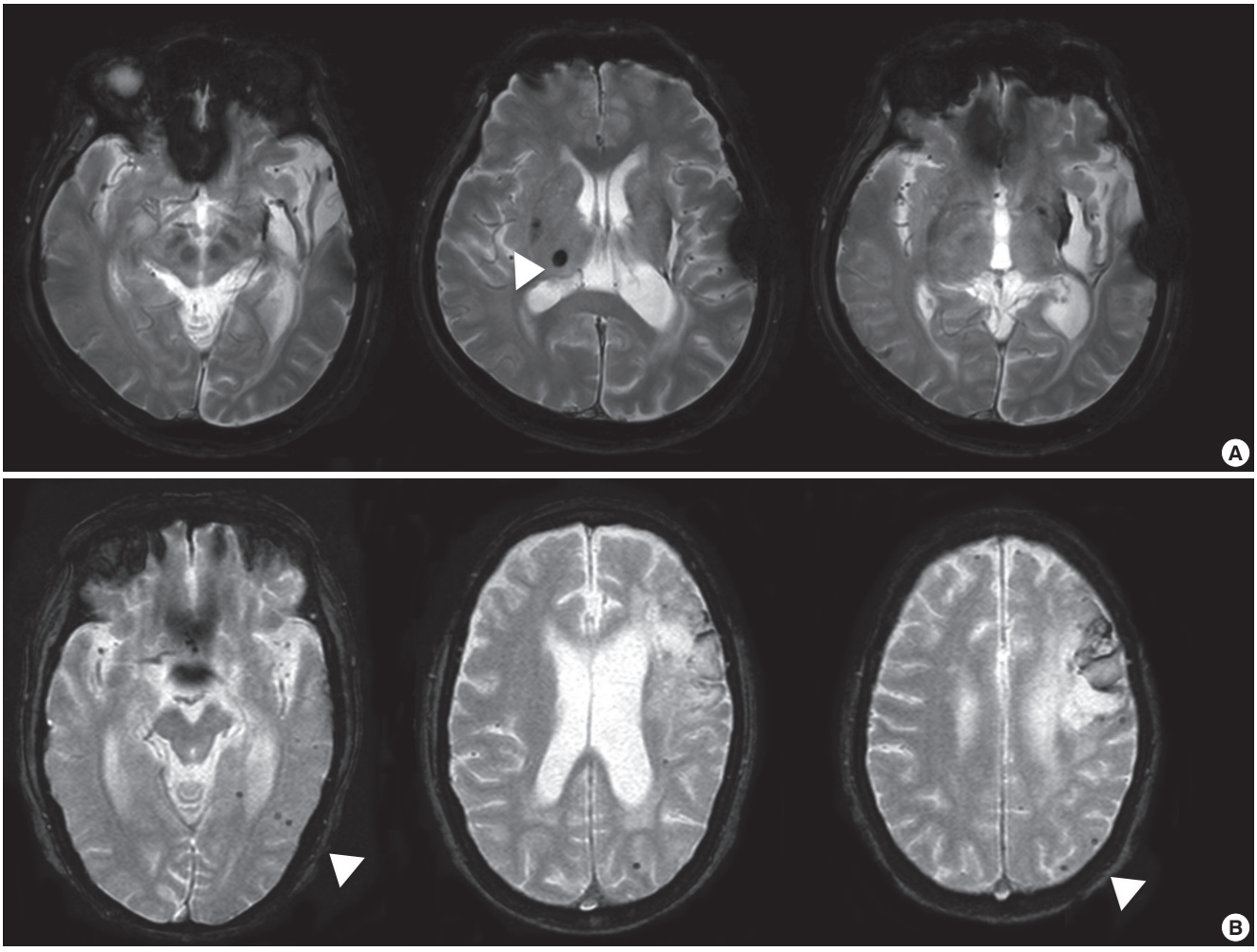

Figure 4. Spatial distribution of cerebral microbleeds by location of hemorrhagic stroke. A case of basal ganglia cerebral hemorrhage with thalamic microbleed (A), compared to a case of lobar hemorrhage with multiple lobar microbleeds (B) in a patient with possible cerebral amyloid angiopathy.

portional to the elevated risk of a future hemorrhagic stroke.[54] The increased risk of hemorrhagic stroke conferred by the presence of CMBs was also confirmed in a prospective study of 112 ICH survivors.[65] Furthermore, association between CMBs and larger ICH volume has been suggested by two studies,[9,66] and the predictive value of CMBs in ICH in patients with advanced white matter lesions also has been documented.[67] The spot sign, an enhancing locus of contrast extravasation in a cerebral hematoma, suggesting ongoing bleeding, was reported to be negatively associated with the number of microbleeds; this result is not consistent with previous findings, and bears further investigation.[68] Patients with CMBs also have been reported to be 2.8 times more likely to have a subsequent disabling or fatal stroke.[69] A systematic review published in 2013 concluded that the presence of CMBs in patients with ischemic stroke was associated with greatly increased odds of a subsequent hemorrhagic stroke, but was only modestly linked to recurrence of ischemic stroke.[56] This meta-analysis also noted that the strength of association between CMBs and subsequent ICH risk was modified by ethnic background, with a greater odds ratio in Asian cohorts than in Western cohorts (Figure 5).

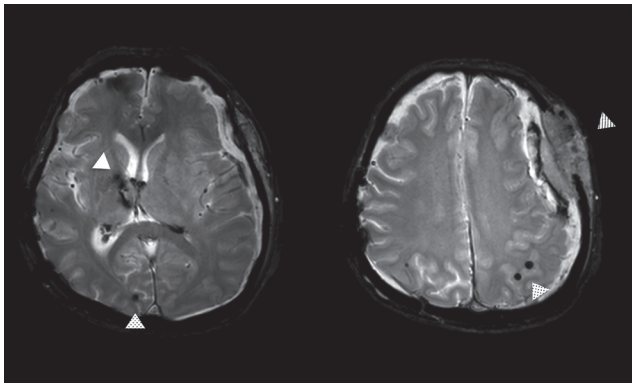

Figure 5. A basal ganglia intracerebral hemorrhage (white arrow) in a patient with a few lobar cerebral microbleeds (dotted arrow). The patient took an antiplatelet medication for several months and developed a subdural hemorrhage (hatched arrow).

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The increased likelihood of cerebral hemorrhage associated with the presence of CMBs may allow prediction of hemorrhagic transformation after ischemic stroke. An earlier report suggested that hemorrhagic transformation after thrombolysis was associated with the presence of CMBs.[70] In a case series of 100 acute ischemic stroke patients with imaging follow-up, the presence of CMBs was indicative of early hemorrhagic transformation.[71] Embolic ischemic strokes occurring at the sites of previous CMBs were noted to become hemorrhagic.[63] Contrary to these positive associations, however, a retrospective study of 279 acute ischemic stroke patients reported no association between CMB count and subsequent hemorrhagic transformation,[72] and in an analysis of 70 stroke patients on thrombolytic treatment, CMBs failed to predict post-thrombolytic hemorrhagic transformation.[73] No relationship between CMBs and prediction of hemorrhagic transformation was observed in a group of 1,034 acute ischemic stroke patients recruited in a single hospital.[74] Finally, a pooled analysis of 570 acute ischemic stroke patients from 13 centers in Europe, North America, and Asia reported that symptomatic ICH after thrombolytic treatment developed regardless of the initial CMB frequency or extent.[75] These studies suggest that for patients in need of thrombolysis, any increased risk of ICH attributable to CMBs is negligible, and unlikely to exceed the benefits from thrombolytic therapy. A subsequent meta-analysis indicated that the published analyses were vulnerable to publication bias and limited power, and identified a trend toward increased odds of symptomatic hemorrhage after thrombolysis (odds ratio, 1.98; 95% confidence interval 0.90-4.35).[76] At present, identification of CMBs on baseline GRE images should not be considered a contraindication to thrombolysis treatment, but further investigation is warranted on this important issue.

Different findings regarding CMBs and the development of ICH or hemorrhagic transformation may be explained by the different pathological mechanisms of the two phenomena. Essentially, ICH involves rupture of a fragile microvascular wall affected by lipohyalinosis or microaneurysms under the chronic influence of hypertension.[77] As CMBs have histological characteristics similar to those of vasculopathy, a correspondingly similar mechanism may underlie formation of CMBs and ICHs.[22] In contrast, hemorrhagic transformation develops after acute lethal injury in relatively healthy microvasculature.

Considerable interest also exists in utilizing detection of CMBs to estimate the risks of hemorrhagic complications in patients on antithrombotic treatment. Two patients on warfarin were reported to have developed lobar hemorrhages right at the location of CMBs.[64] I CMBs were found to be more frequent and extensive in patients with aspirin-associated ICH.[11,78] In a cross-sectional study, CMBs were more common in patients taking antithrombotic agents, and aspirin use was found to be related to a lobar location.[79] Results from our group demonstrated that patients with anticoagulation-associated hemorrhagic stroke complications are 3.6 times more likely to have CMBs than are age- and sex-matched controls.[12] A recent pooled analysis involving 1,460 hemorrhagic strokes and 3,817 ischemic strokes concluded that the number of CMBs was greater in warfarin users who developed ICH.[80] Given the strong association between CMBs and subsequent ICHs in stroke survivors, a prospective study is needed to assess the predictive power of CMBs in stroke patients on antithrombotic treatment.

Conclusion

CMBs were first identified as tiny, round dark-signal lesions on GRE MRI, and are frequently detected in patients with ischemic or hemorrhagic strokes. Pathological analysis demonstrated that CMBs are extravasations of blood components through fragile microvascular walls, and therefore reflect a bleeding-prone vasculopathy in brain. Several clinical studies have concluded that CMBs are associated with hemorrhagic stroke and hemorrhagic complications following antithrombotic medications. The currently available data do not support the exclusion of thrombolytic treatment based solely on CMB presence or extent. Prospective studies are warranted to confirm the clinical implications of CMBs, and to establish their use for predictive models of hemorrhagic stroke in various situations.

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