Brain Microbleeds: Distribution and Influence on Hematoma and Perihematomal Edema in Patients with Primary Intracerebral Hemorrhage

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SUMMARY – *Brain microbleed is a marker of small vessel microhemorrhagic or microaneurysmal lesions, which may induce intracerebral hemorrhage (ICH). This study to prospectively evaluated the association between microbleeds, hematoma and perihematomal edema volume, and various clinical data, as well as patient outcome. Thirty-one patients with ICH and 31 healthy age-matched subjects were enrolled in our study. They were divided into two groups according to the presence or absence of microbleeds detected by MRI. Serial clinical and laboratory data were recorded. Modified Rankin Scale and Barthel Index were estimated three months after hemorrhage. The major location of microbleeds among patients with ICH was the basal ganglia. The volume of perihematomal edema was correlated with the initial hematoma volume on the first, fifth and seventh days after hemorrhage in patients with microbleeds. For patients without microbleeds, this correlation was also significant on the seventh day. Cerebral microbleeds in patients with ICH, especially in the basal ganglia region, represent micro-angiopathy, and are associated with leakage of blood and formation of perihemorrhage edema. Brain microbleeds found in patients with ICH warrant further investigation for evaluation of stroke risk.*

Introduction

Primary intracerebral hemorrhage (ICH) is estimated to affect more than one million people worldwide each year, most of whom either die or are left seriously disabled. One of the reasons for the relatively poor outcomes for ICH is the elevation of intracranial pressure due to the mass effect from the hematoma and perihematomal edema. The elevated intracranial pressure may eventually result in decreased cerebral perfusion or tissue shifts and herniation syndromes. Moreover, the coagulation cascade is activated after ICH, and atypical neurotoxins from breakdown of hemoglobin and the inflammatory process are also responsible for neurological deterioration when the patient has suffered an ICH [1]. However, the clinical diagnosis of ICH does not always accurately reflect the underlying etiology which may include cerebral amyloid angiopathy or hypertensive vasculopathy, which may have begun several years before the acute ICH.

Brain microbleeds (BMBs) were first described in the mid-1990s. A microbleed is defined as a rounded focus <5 mm in diameter that is hypointense on T2*-weighted, gradient-echo sequences or DWI, which are highly

sensitive to paramagnetic substances such as deoxyhemoglobin, a product of blood degradation, or ferritin, a non-heme iron. A microbleed is distinguishable from other intracerebral hematomas, but is indistinct from flow voids, leptomeningeal hemosiderosis, and non-hemorrhagic subcortical mineralization. In such cases, reduction in the MRI signal is usually caused by hemosiderin deposits [2]. Although BMBs are generally considered clinically silent, growing literature evidence supports the idea that BMBs are a marker of small vessel microhemorrhagic or microaneurysmal lesions, which may be of particular interest in elucidating the causes of macroscopic ICH [3-5]. However, few studies have investigated the prevalence and spatial distribution of BMBs in relation to the factors associated with outcome after ICH.

This study undertook a prospective MRI evaluation of BMB prevalence in ICH patients to elucidate the associations between BMBs, various clinical data, imaging findings, and patient outcome.

Material and Methods

Patients

Thirty-one patients admitted to our institution within 24 hours after onset of symptoms due to acute ICH were enrolled in this study. Patients were enrolled after ICH was confirmed by initial CT scan. Exclusion criteria were: large hematomas requiring emergency surgery, history or CT findings of old ICH, or other neurological insult, and evidence of intraventricular hemorrhage on initial CT scan. Thirty-one healthy age- and gender-matched subjects were also enrolled. Patients were divided into two groups according to whether they had BMBs detected by MRI. All subjects or their family informants were prospectively interviewed for clinical data including history of diabetes mellitus (DM), coronary artery disease (CAD), hypertension (HTN), or any other neurological deficits.

Laboratory studies including serum glucose, alanine transaminase (ALT), blood urea nitrogen (BUN), creatinine (Cr), triglycerides (TG), cholesterol (Chol), white blood cell count (WBC), hemoglobin (Hgb), platelet count (PLT), low density lipoprotein (LDL), glycated hemoglobin (HbA1c) were recorded as the first levels drawn. Time of symptom onset was defined as the last time the patient was known to be symptom-free. NIHSS and Glasgow Coma Scale (GCS) were estimated by two experienced neurosurgeons (T-Y.Y and M-H.L) within 24 hours after ICH. Modified Ranking Scale (mRS) and Barthel Index (BI) were estimated by the same neurosurgeons at three months after ICH. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and all patients gave written informed consent.

MRI

Magnetic resonance imaging scans were obtained with a 1.5T human MRI scanner (GyroscanIntera; Philips Medical Systems. Best, The Netherlands) at baseline (within 24 hours) and at five and seven days after onset of symptoms. Standard sequences for depiction of anatomy, hematoma, and extent of edema as well as microbleeders included axial T2*-weighted gradient echo images for location and volume of the hematoma as well as presentation of BMBs (repetition time [TR]/echo time [TE] = 355/13. 81 ms, excitations = 1, flip angle = 18º, section thickness = 6. 5 mm with a gap = 1. 5 mm and matrix = 512 × 256) and axial fluid-attenuated inversion recovery (FLAIR) images for extension of perihematomal edema ([TR]/[TE] = 6000/120 ms, excitations = 2, flip angle = 90º, same section thickness and matrix).

Statistical Analysis

To validate the reliability of T2*-weighted gradient echo images for detection of BMBs number and location, and to learn which can give the same result on different occasions (intra-observer reliability) or between different neuroradiologists (inter-observer reliability), the contribution of estimated number and locations of BMBs were estimated by one radiologist (W-M.L) on different occasions and by two radiologists (W-M.L and Y-H.T) with intraclass correlation coefficients (ICC). A one-way ICC with absolute agreement was used to assess intra-observer reliability, and a two-way ICC with absolute agreement was used to examine inter-observer reliability. The numeric variables are presented as means with standard deviation or corresponding 95% Cis, and were compared by performing the unpaired t test. Categorical or ordinal variables were compared by means of the Fisher's exact test as appropriate. Performance characteristics of each variable, including sensitivity and specificity,

Table 1 Demographic characteristics of ICH patients with and without BMBs.

	with BMBs (n=22)	*without BMBs (n=9)*	P *value*
Age	67.6	57.8	0.1282
Male gender	13	6	0.7077
Waistline (cm)	87.8	83.1	0.3494
History of Hypertension	16	8	0.2864
History of Diabetes	2	2	0.4287
History of Cardiovascular Disease	2	0	0.1621
History of Stroke	2	1	0.8766
History of Smoking	3	4	0.2219
Blood glucose (mmol/L)	136.1	139.7	0.7997
Alanine transaminase (ALT) units/litre	27.4	36.1	0.4919
Triglycerides (TG) mg/dl	152.9	95.3	0.4259
Cholesterol (Chol) mg/dl	147.8	204.3	0.1697
White blood cell count (WBC) mm^3	7.9	8.9	0.3917
Glycated hemoglobin (HgbA1C) mg/dl	14.1	14.7	0.3055
Platelet count (PLT) ($\times 10^6$/Lite)	220.1	227.1	0.8125
Low density lipoprotein (LDL) mg/dl	110.6	136.7	0.1887
HbAlc (%)	6.0	6.2	0.8662
Day 1 NIHSS[1] score	11.6	9.6	0.3024
Day 1 GCS[2] score	12.5	14.0	0.0884
MRS[3] after 3 months	2.9	2.4	0.3513
BI[4] after 3 months	6.2	4.5	0.5424

*1 National Institutes of Health Stroke Scale (NIHSS).
*2 Glasgow Coma Scale (GCS).
*3 Modified Rankin Scale (MRS).
*4 Barthel Index (BI).

were calculated. For all statistical analyses, statistical significance was set at $P < 0.05$. All statistical analysis used were SAS Enterprise Guide 4 and JMP 4 (SAS Inc.).

Results

Two representative cases of ICH patients with BMBs are shown in Figure 1. The incidence of BMBs was 70.9% in patients with ICH, and 9.6% in otherwise healthy subjects. The demographic data for ICH patients are shown in Table 1. There was no significant correlation between the presence of BMBs and age, gender, or previous illness such as HTN, DM, or stroke. Laboratory examinations, including serum glucose level, ALT, BUN, Cr, WBC, platelet count, Hb, HbA1c; and clinical stroke scales including NIHSS score, CGS score upon arrival in the ED on day 1, and follow-up mRS and BI were also without significant difference between the two groups.

The most prevalent location of BMBs among ICH patients was the basal ganglia, whether assessed on the first, fifth or seventh day (P=0.0151, 0.0026, and 0.0054 on the first, fifth and seventh days, respectively; Table 2).

Table 3 shows the correlation between the total volume of the lesion, including edema and hematoma (V), the volume of hematoma (H), and the volume of perihematomal edema (PE). The total volume of lesion and the volume of hematoma on day 1 are related to volumes of perihematomal edema in patients with BMBs on the first, fifth and seventh days after ICH. In patients without BMBs, the volume of perihematomal edema was associated only with the total lesion volume on the seventh day.

Discussion

Brain microbleeds have been increasingly recognized since the advent of modern MRI imaging techniques. However, in clinical prac-

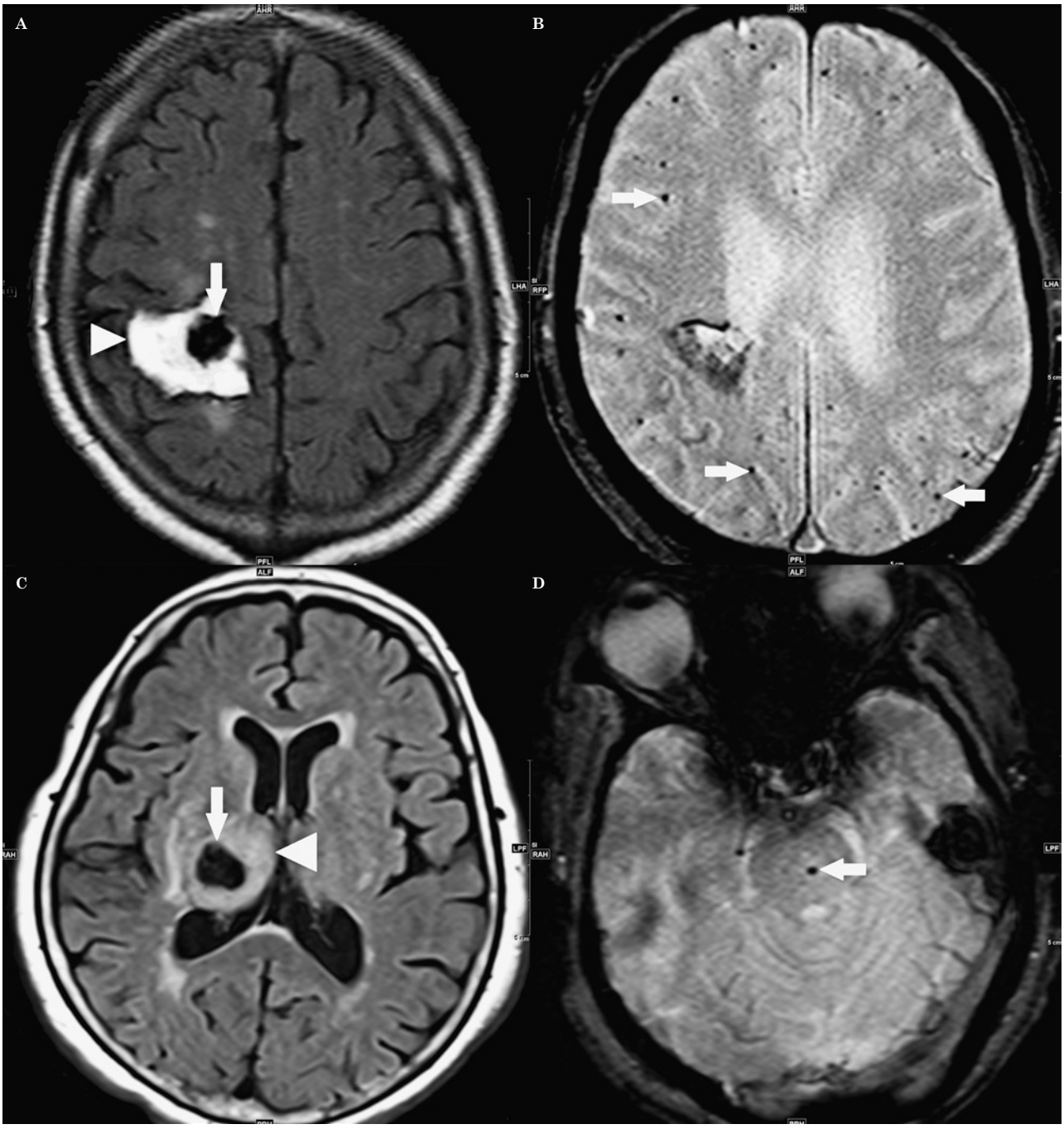

Figure 1 Illustrative fluid-attenuated inversion recovery (FLAIR) and axial T2*-weighted gradient echo (GRE) images in two cases. A,B) An 80-year-old man with weakness of the left limbs. FLAIR (A) showed right parietal hematoma (arrow) with perihematomal edema (arrowhead). GRE (B) showed numerous lobar microbleeds (arrows). C,D) A 77-year-old woman with weakness of the left limbs. FLAIR (C) showed right thalamic hematoma (arrow) with perihematomal edema (arrowhead). GRE (D) showed a single microbleed in the pons (arrow).

tice, their diagnostic value, associated risks, and prognostic significance remain to be determined. BMBs are commonly found in patients admitted with stroke, and in the general elderly population on gradient-echo (GE) or T2*-weighted MRI sequences. Silent BMBs occur in 3%-6% of otherwise healthy elderly subjects [6], and the prevalence gradually increases with age from 6.5% in the age category 45 to 50 years old to 35.7% among subjects

Table 2 Locations of BMBs in ICH patients.

	Day 1		*Day 5*		*Day 7*	
Locations of BMBs	*chi-square*	P *value*	*chi-square*	P *value*	*chi-square*	P *value*
Frontal	3.044	0.2183	1.879	0.1705	1.879	0.1705
Parietal	2.439	0.2954	3.699	0.1573	3.044	0.2183
Temporal	4.411	0.1102	3.699	0.1573	3.044	0.2183
Occipital	3.044	0.2183	3.699	0.1573	3.044	0.2183
Basal ganglia	10.444*	0.0151*	11.889*	0.0026*	10.444*	0.0054*
Thalamus	2.439	0.2954	2.439	0.2954	1.879	0.1705
Infra-tentorial	0.423	0.5156	0.875	0.3497	1.359	0.2438
Brainstem	1.879	0.1705	2.439	0.1184	1.879	0.1705

*P value<0.05.

Table 3 Correlation of BMBs-associated parameters in ICH patients.

	Parameters 1	*Parameters 2*	*with BMBs (n=22)*		*without BMBs (n=9)*	
			Spearman's ρ	P *value*	*Spearman's* ρ	P *value*
Day 1	Edema	Day 1 V	0.9447	<0.0001*	0.45	0.2242
	Edema	Day 1 H	0.8058	<0.0001*	0.1167	0.765
Day 5	Edema	Day 1 V	0.8159	<0.0001*	0.65	0.0581
	Edema	Day 1 H	0.6364	0.0015*	0.3167	0.4064
Day 7	Edema	Day 1 V	0.8137	<0.0001*	0.85	0.0037*
	Edema	Day 1 H	0.6307	0.0016*	0.6	0.0876

V: total volume of lesion, including hematoma and edema; *H*: volume of hematoma; *Edema*: volume of perihematomal edema; *D1*: first day after ICH
*P value<0.05

80 years of age. In the United States, BMBs were found in 20% of patients with ischemic stroke, and in 54%-71% of patients with acute spontaneous ICH. The clinical history of male gender, cigarette smoking, and white matter disease are also recognized as factors associated with BMBs. In addition, BMBs are found in a greater overall proportion of Asian stroke patients, as described by Jeerakathil et al.[7]. In this study, the incidence of BMBs in ICH patient was 71%, which is higher than noted in previous publications. This is probably due to the older age of our patients (mean: 67.6 years of age). There was no significant association between BMBs and age, gender, hypertension, or diabetes mellitus. This observation is in accord with that of a previous report[6]. The results of laboratory studies, including factors associated with coagulopathy such as BUN, Cr, ALT, and platelet count; those associated with risk of CAD such as TG, cholesterol, and LDL; studies associated with inflammation and edema such as WBC; and clinical assessments such as GCS, NIHSS on day 1 and after three months, MRS, and BI, all lacked a significant association with BMBs.

The location of BMBs is believed to be associated with underlying vascular pathology. BMBs found in deep or infratentorial regions are associated with known risk factors for hypertensive vasculopathy whereas cortical-subcortical BMBs represent underlying cerebral amyloid angiopathy[8]. For ICH patients, 39% of BMBs were found to be in cortical-subcortical regions, and 38% in the basal ganglia or thalamus[6]. Deep and subcortical BMBs are found to be a risk factor for the development of non-hypertensive deep ICH[9], and posterior fossa hemorrhage is a predictor of poor outcome in adult patients[10]. In this study, BMBs were preferentially seen in the basal ganglion area (P value<0.001) compared with lobar hemi-

spheres. This result is similar to that of Lee et al. who claim that brain BMBs are regionally associated with intracerebral hemorrhage [11].

Perihematomal edema plays an important role in secondary brain injury after ICH [12]. PE develops within three hours of onset of symptoms in most patients, and reaches its maximum between ten and 20 days after ICH and is directly related to hematoma volume. However, the association between BMBs and PE has not been clearly defined. In our study, the volume of PE on the first, fifth and seventh days was significantly related to the total volume of hematoma and hemorrhage after the onset of ICH in patients with co-existing BMBs ($P<0.05$). In patients without BMBs, edema volume was associated only with the total volume of the lesion on the seventh day. We propose that BMBs might be an important predictor of increase in edema and total lesion volumes at an early stage.

Multiple mechanisms are involved in the development of brain edema after ICH. These include a very early phase (first few hours) involving hydrostatic pressure and clot retraction, a second phase (first two days) involving activation of the coagulation cascade and thrombin production, and a third phase (after three days) involving RBC lysis and hemoglobin-induced neuronal toxicity [1]. The products of hemoglobin degradation can release iron, and can contribute to brain edema formation [13]. A recent study found a significant positive correlation between serum ferritin and the relative volume of perihematomal edema on days 3 and 4 in patients with spontaneous ICH [14]. Another study revealed that deferoxamine, an iron chelator, can reduce hematoma- and hemoglobin-induced edema, suggesting that iron plays an important role in edema formation after ICH [15]. Degradation of hemoglobin contained in erythrocytes results in the formation of hemosiderin, which is paramagnetic and is the key compound underlying magnetic susceptibility effects that allow BMBs to be detected by MRI. Based on these reports and our results, we hypothesize that the BMBs are marker of small vessel pathology that can represent a tendency for RBC lysis and hemoglobin leakage following ICH, and thus is associated with lesion extension and with damage caused by PE.

There are several limitations to this study. First, our results were derived from a small sample size, and further group analysis could not be carried out. Second, because PE peaks between ten and 20 days after ICH in humans, an additional MRI scan at this time point may have provided more information.

Conclusion

The role of the BMBs in ICH patients is still under investigation. In the current study, the most common location of BMBs in ICH patients was the basal ganglia. Cerebral microbleeds in patients with intracerebral hemorrhage may represent micro-angiopathy, and are associated with leakage of blood, and the formation of perihemorrhage edema. When MRI reveals BMBs in the evaluation of a patient with ICH, this finding warrants further investigation for evaluation of stroke risk.

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