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Cerebral Microbleeds: Histopathological Correlation of Neuroimaging

A. Shoamanesh[a] C.S. Kwok[c] O. Benavente[a, b]

[a]Division of Neurology, Department of Medicine, and [b]Brain Research Center, UBC Hospital, University of British Columbia, Vancouver, B.C., Canada; [c]School of Medicine, Health Policy and Practice, Health and Social Sciences Research Institute, Faculty of Health, University of East Anglia, Norwich, UK

Key Words
Microbleeds · Microhaemorrhage · Microhemorrhage · Pathology · Histology · Histopathology

Abstract
Background: In recent years, there has been a growing interest in cerebral microbleeds (CMBs) and their role in cerebrovascular disease. A few studies have investigated the histopathological correlation between CMBs and neuroimaging findings. We conducted a systematic review in an attempt to characterize the pathological and radiological correlation. ***Methods:*** A systematic literature search was conducted for studies in which CMBs were characterized histopathologically and correlated with MRI findings. ***Results:*** Five studies met the inclusion criteria, with a total of 18 patients. Hemosiderin deposition was reported in 42 CMBs (49%), while 16 CMBs (19%) were described as old hematomas which stained for iron, 13 (15%) had no associated specific pathology, 11 (13%) contained intact erythrocytes, 1 (1%) was due to vascular pseudocalcification, 1 (1%) was a microaneurysm and 1 (1%) was a distended dissected vessel. Lipofibrohyalinosis was the most prominent associated vascular finding. Amyloid angiopathy was present primarily in patients with dementia. ***Conclusions:*** Although histopathological associations have been observed using MRI in patients with CMBs, the findings have yet to be validated and further research is warranted.

Introduction

Cerebral microbleeds (CMBs) are defined as small round hypointense foci on T2*-weighted gradient-recalled echo (GRE) magnetic resonance imaging (MRI) and are believed to represent hemosiderin deposits that can remain in macrophages for years following a microhemorrhage. In recent years, there has been an exponentially growing interest in determining the clinical significance of CMBs. Yet, there have only been a few studies investigating the histopathological correlation of CMBs as defined by neuroimaging. Histopathological confirmation of CMBs seen on neuroimaging is important because there are a number of CMB mimics. It is thus prudent to ensure that the contemporary studies on CMBs, which are being performed under the assumption that the hypointensities seen on MRI represent areas of old microhemorrhage, are not done so in vain.

Recently, Gouw et al. [1] published a systematic review of the histopathology of MRI findings in small vessel disease that comments on CMBs. However, as CMBs were not the main focus of their paper, there has yet to be a review solely on the histopathology of CMBs. We conducted a systematic review focusing exclusively on the relationship between CMBs observed on neuroimaging and correlated analysis of histopathological samples, resulting in a more detailed analysis of the topic.

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Ashkan Shoamanesh, MD
Division of Neurology, Department of Medicine
University of British Columbia, 1103-1068 West Broadway Ave
Vancouver, BC V6H 0A7 (Canada)
Tel. +1 778 847 6338, E-Mail ashkan.sho@gmail.com

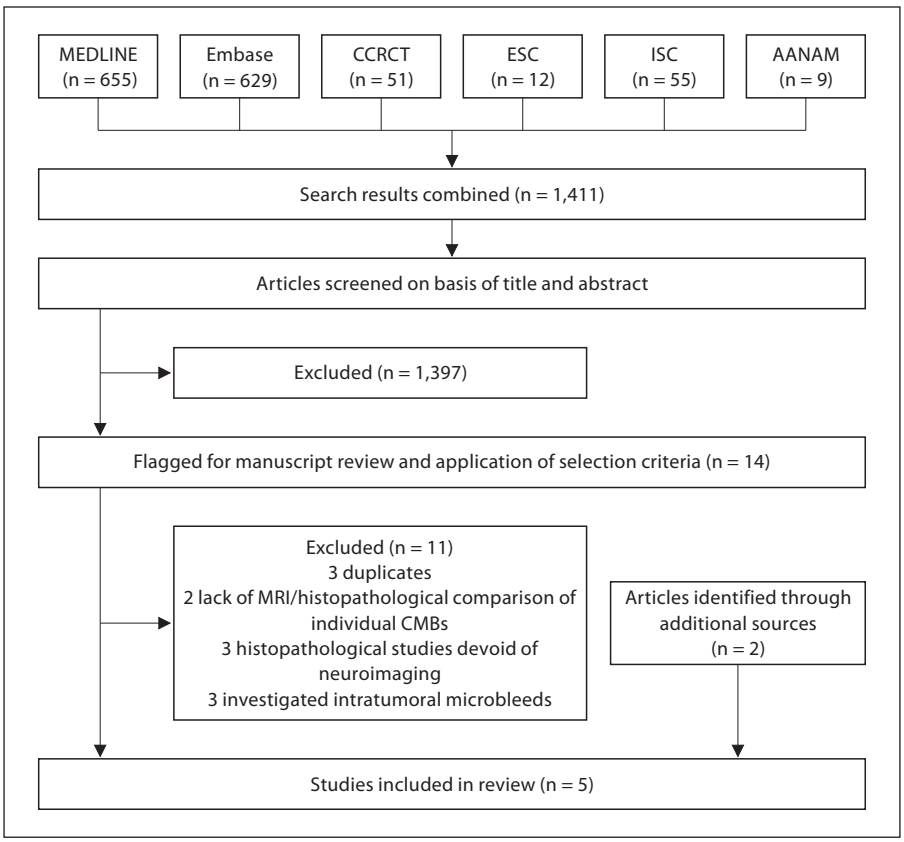

Fig. 1. Flow diagram of our literature search and study selection. CCRT = Cochrane Central Register of Controlled Trials; ESC = European Stroke Conference; ISC = International Stroke Conference; AANAM = American Academy of Neurology Annual Meeting.

Methods

Wherever applicable, we adhered to previously published guidelines on conducting systematic reviews of diagnostic studies [2]. A systematic literature search was performed by one of the authors (C.S.K.). A comprehensive search strategy is provided within the Appendix.

One reviewer (A.S.) scanned all titles and abstracts for studies that met the predetermined selection criteria and extracted the relevant data (fig. 1). Human studies in which CMBs, as defined by T2*-weighted GRE MRI, were investigated by histopathology and which provided a direct comparison of MRI and histopathology for individual lesions were eligible. Those studies investigating CMBs >10 mm in diameter, intratumoral microbleeds or patients with head trauma were excluded. The accuracy of the extracted data was confirmed independently by another reviewer (O.B.).

Histopathological evidence of a previous microbleed was defined as any site that contained hemosiderin-laden macrophages, hemosiderin deposits, erythrocytes or hematoma formation.

Table 1. Histopathological stains used in reviewed studies

Study	Stains
Fazekas et al., 1999 [3]	hematoxylin and eosin, Masson trichrome, Kluver-Barrera technique for myelin, Congo red for amyloid and with iron
Tanaka et al., 1999 [4]	hematoxylin and eosin, Masson trichrome, Kluver-Barrera technique for myelin
Kikuta et al., 2007 [5]	immunostaining with antibodies against human factor VIII and human α-smooth muscle actin
Tatsumi et al., 2008 [6]	hematoxylin and eosin, Prussian blue for iron
Schrag et al., 2009 [7]	hematoxylin and eosin, Prussian blue for iron

Results

We identified 5 studies that met our predetermined criteria. The first and largest study, published by Fazekas et al. [3] in 1999, was the only study that comments on the blinding of investigators conducting histopathological analysis to neuroimaging findings in their methodology.

Although histopathological stains were generally homogenous amongst the studies (table 1), MRI parameters varied greatly and are summarized in table 2 [3–7]. The

Table 2. MRI parameters

Study	Timing of MRI/tissue preparation prior to imaging	Field strength T	Sequence	Slice thickness, mm	TR, ms	TE, ms	Flip angle degrees
Fazekas et al., 1999 [3]	postmortem/ fixed in formalin	1.5	GRE	5	550–650	15	25
Tanaka et al., 1999 [4]	antemortem/NA	1	GRE	not specified	2,178–2,190	36–37	25
Kikuta et al., 2007 [5]	antemortem/NA	3	T2-weighted (not specified)	not specified	not specified	not specified	not specified
Tatsumi et al., 2008 [6]	postmortem/fixed in formalin, imaged in water	1.5	GRE	3	700	17	20
Schrag et al., 2009 [7]	postmortem/fixed in formalin, imaged embedded in 4% agarose gel	3	GRE (SWI)	2	30	20	15

NA = Not applicable.

upper limit of CMB diameter was defined as 5 mm in two studies [3, 6], 5.7 mm in one [7] and 10 mm in another [5]. Tanaka et al. [4] did not define a specific parameter but did comment that the majority of CMBs had a diameter within the range of 2–5 mm. In total, the studies included 26 patients. Four patients in the study by Fazekas et al. [3] and 4 in that by Schrag et al. [7] did not have any CMBs visualized on neuroimaging [3, 7]. Moreover, 2 of the CMBs in the study by Kikuta et al. [5] were never investigated by histopathology. Thus, the association between CMBs seen on imaging and their histopathology has been investigated in a total of 18 patients, encompassing 85 lesions.

The mean age of the patients was 73 years, and 56% were men (table 3). Hypertension was present in 44%, in whom 82.5% (33/40) of CMBs were located in the subcortical gray matter, brainstem or cerebellum. In contrast, amongst nonhypertensives (n = 10), 6 of whom had documented dementia, 76.6% (36/47) of lesions were corticosubcortical.

Histopathology of CMBs

Fazekas et al. [3] demonstrated that in 7 patients with previous intracerebral hemorrhage (ICH), 21 out of 34 CMBs contained hemosiderin-laden macrophages (table 4). These were often perivascular. In the remaining 13 CMBs, no specific pathology was found. In the 3 different cases with various causes of death investigated by Tanaka et al. [4], all 3 CMBs demonstrated hemosiderin deposits in the perivascular space. However, one lesion also had an associated organized pseudoaneurysm. An autopsy study of a 97-year-old woman who died following an ischemic stroke demonstrated hemosiderin-laden macrophages in 8 of 9 CMBs [6]. The underlying pathology of the remaining lesion was vascular pseudocalcification. One CMB resected from the right frontal operculum in a 65-year-old male with presumed moyamoya disease during a superficial temporal artery-middle cerebral artery bypass procedure revealed an encapsulated hematoma containing erythrocyte deposition [5]. There was no mention of the presence or absence of hemosiderin.

The 6 cases with a diagnosis of Alzheimer's disease [7] had 38 CMBs visualized on susceptibility-weighted imaging (SWI). Sixteen of these lesions were described as old hematomas which stained for iron, 10 lesions contained intact erythrocytes, 7 revealed cavitary lesions which were associated with a gliotic capsule containing hemosiderin granules and hemosiderin-laden macrophages, 3 contained hemosiderin granules and hematoidin deposition, 1 was a microaneurysm and another a dissection in the wall of a grossly distended vessel. The cavitary lesions were occasionally associated with a characteristic hyperintense halo surrounding the hypodensity on SWI, particularly in the deep white matter.

Vascular and Other Associated Pathology

Lipofibrohyalinosis seems to be the most prominent vascular finding in relation to CMBs and was present in all of the patients investigated by Fazekas et al. [3]. Two of their patients also displayed moderate to severe amyloid

Table 3. Patient demographics and MRI findings

Case	Age/ sex	Patient population and/or cause of death	HTN	Previous ICH	Lacunae	Cortical strokes	White matter hyperintensity grade	Cortico-subcortical CMBs	Basal ganglia/ thalamic CMBs	Infra-tentorial CMBs
1 [3]	64/M	ICH	–	lobar	–	–	0[a]	2	0	0
2 [3]	74/M	ICH	+	basal ganglia, thalamus	++	–	3[a]	3	4	0
3 [3]	74/M	ICH	+	lobar	++	+	2[a]	1	4	2
4 [3]	84/F	ICH	+	brainstem	+	–	0[a]	0	7	5
5 [3]	71/M	ICH	–	lobar	–	–	2[a]	1	1	1
6 [3]	74/F	ICH	+	lobar	+	–	2[a]	1	0	0
7 [3]	58/M	ICH	+	thalamus	++	–	3[a]	1	1	0
8 [4]	66/F	B cell lymphoma, pneumonia	–	–	–	–	NA	1	0	0
9 [4]	67/M	HTLVI myelopathy, pneumonia	+	–	++	–	NA	0	1	0
10 [4]	50/M	SAH	+	–	+	–	NA	0	1	0
11 [5]	65/M	moyamoya disease	–	–	–	–	NA	3	0	0
12 [6]	97/F	ischemic stroke, gastric cancer	+	–	++	+	mild[b]	1	5	3
13 [7]	61/M	dementia (2 years/rapidly progressive), malnutrition	–	NA	NA	NA	NA	5	0	0
14 [7]	85/F	dementia (slowly progressive), CAD	–	NA	NA	NA	NA	4	1	0
15 [7]	73/F	dementia (severe)	–	NA	NA	NA	NA	3	0	0
16 [7]	90/M	dementia (severe/slowly progressive), pneumonia	–	NA	NA	NA	NA	4	1	0
17 [7]	74/F	dementia (severe/slowly progressive), ICH	–	lobar	NA	NA	NA	9	2	0
18 [7]	86/F	dementia (8 years/slowly progressive), pneumonia	–	NA	NA	NA	NA	4	1	4

HTN = Hypertension; HTLVI = human T lymphocytic virus I; SAH = subarachnoid hemorrhage; CAD = coronary artery disease; NA = not assessed or not provided; + designates presence of; – designates absence of; ++ designates multiple (>1).

[a] White matter hyperintensity grade as per Fazekas et al. [8] on postmortem MRI.

[b] White matter hyperintensity noted on antemortem MRI.

Table 4. Histopathological correlation of neuroimaging

Study	CMBs investigated	Histopathology of CMBs (n)	Associated vascular pathology	'Blooming effect'
Fazekas et al., 1999 [3]	34	hemosiderin-laden macrophages (21), no specific pathology (13)	lipofibrohyalinosis, amyloid angiopathy	NA
Tanaka et al., 1999 [4]	3	hemosiderin deposits (3), organized pseudoaneurysm (1)	arteriosclerotic microvessels	NA
Kikuta et al., 2007 [5]	1	encapsulated hematoma containing erythrocyte deposition (1)	arterioles with disrupted internal elastic lamina	NA
Tatsumi et al., 2008 [6]	9	hemosiderin-laden macrophages (8), vascular pseudocalcification (1)	lipohyalinosis, microaneurysm formation	insignificant
Schrag et al., 2009 [7]	38	old hematomas which stained for iron (16), intact erythrocytes (10), cavitary lesions with a gliotic capsule containing hemosiderin granules and hemosiderin-laden macrophages (7), hemosiderin granules and hematoidin deposition (3), microaneurysm (1), dissection in the wall of a distended vessel (1)	amyloid angiopathy, microaneurysm formation	1.57 ± 0.75 times larger, greatest in smaller CMBs, maximum magnitude of 3

NA = Not assessed.

angiopathy. Case 1 (table 3) was a nonhypertensive patient who had only experienced lobar ICHs and corticosubcortical CMBs. The other patient (case 2) was hypertensive and had also experienced a deep gray matter ICH and deep gray matter CMBs, in addition to cortico-subcortical ones. All 3 patients investigated by Tanaka et al. [4] were noted to have arteriosclerotic microvessels. The 97-year-old woman studied by Tatsumi et al. [6] displayed lipohyalinosis and microaneurysm formation. However, Schrag et al. [7] found most lesions in demented patients to contain evidence of cerebral amyloid angiopathy with vessel wall thickening, β-amyloid replacement of vascular smooth muscle and microaneurysms. The CMB in the patient with moyamoya disease contained arterioles with a disrupted internal elastic lamina.

Varying degrees of tissue rarefaction and gliosis, as well as lacunar infarction and a cribriform state of the basal ganglia, were observed in these studies [3–7].

'Blooming Effect'

The 'blooming effect', where MRI overestimates the diameter of a microbleed, was described in two studies (table 4). When using SWI [repetition time (TR)/echo time (TE): 30/20 ms, flip angle 15°], CMBs were 1.57 ± 0.75 times larger than their corresponding lesion on pathology [7]. The magnitude of 'blooming' was greater for smaller lesions. In contrast, Tatsumi et al. [6] found that the size of CMBs on GRE MRI (TR/TE: 700/17 ms, flip angle 20°) and corresponding hemosiderin deposits were roughly similar.

Discussion

Our review of the literature suggests that there is a strong association between CMBs identified on MRI and histopathological evidence of previous hemorrhage, most commonly in the form of hemosiderin-laden macrophages. Eleven lesions (12.9%) in our review were noted to contain erythrocytes, which implies that not all CMBs are chronic in nature.

Recently, De Reuck et al. [9] published a study determining the neuropathological correlates of CMBs on postmortem brain sections from 20 Alzheimer patients using 7-tesla MRI. They investigated 79 hemorrhages of 1–3 mm in diameter on gross pathology and 163 hemorrhages invisible to the naked eye (200–500 μm). They showed the sensitivity and specificity of 7-tesla GRE imaging to be 100 and 50%, respectively, for detecting hemorrhages of 1–3 mm diameter and 100 and 38%, respectively, for smaller hemorrhages (200–500 μm). For the larger lesions, the positive predictive value (PPV) was 96% and the negative predictive value (NPV) was 100%. For lesions of 200–500 μm, the PPV and NPV were 77 and 100%, respectively. False positives consisted of perforating vessels filled with postmortem thrombi or iron and calcium deposits around vessels or in astrocytes. These occurred exclusively in the deep white matter, striatum and internal capsule.

None of the studies within our review were designed to calculate the sensitivity and/or specificity of MRI in detecting CMBs proven on pathology. However, extrapolating from the available data we can make a general estimation. Among the 4 studies which utilized GRE MRI there was histopathological evidence of a hemorrhage in 33 CMBs (true positives). False positives occurred at 13 sites (18.8%). Most of these were from the study by Fazekas et al. [3], in which no other specific pathology was found. This study imaged postmortem whole brains surrounded by air, and it has been argued that the high false-positive rate was likely secondary to air artifacts [6]. Pathologies underlying false-positive CMBs in the other studies included pseudocalcification of a vessel [6], a microaneurysm and a distended dissected vessel [7]. Interestingly, the vascular pseudocalcification (a known CMB mimic) located in the left pallidum of case 12 was an asymmetric finding that did not appear hyperdense on computed tomography (CT) imaging. This lesion would thus be graded as a 'definite' [10] CMB or could possibly be graded as a 'certain' [11] one, according to the currently available CMB rating scales. In view of the above and the frequent occurrence of calcification/mineralization within this region, we propose that unilateral pallidal lesions otherwise fulfilling the definition of a CMB should be graded as either 'possible' [10] or 'uncertain' [11] CMBs irrespective of absent hyperdensity on CT.

False negatives were only commented on in the study by Fazekas et al. [3], in which 20 MRI-negative hemosiderin deposits were isolated, 8 of which were in 2 patients who were completely lacking CMBs on MRI. Thus, exclusively in that study, we can estimate the sensitivity of CMBs on 1.5-tesla GRE MRI (TR/TE: 550–650/15 ms, flip angle 25°) as 51.2% [21/(21 + 20)]. This number is arguably an overestimation, given the lack of proper methodology to isolate false-negative lesions. Without any true-negative values we are unable to estimate the specificity. However, we can estimate the PPV as 61.8% [21/(21 + 13)]. The aforementioned discussion regarding false-positive lesions in this study would imply that this might be an underestimation.

Assuming that the 7 cavitary lesions in the study by Schrag et al. [7] using 3-tesla SWI represent tissue necrosis secondary to hemorrhage, there were only 2 false positives within the 38 CMBs visualized. The PPV in this study can thus be estimated at 94.7% [36/(36 + 2)]. This higher PPV in comparison to that of Fazekas et al. [3] is potentially a reflection of the minimization of air artifacts by embedding formalin-fixed brain slices in blocks of 4% agarose gel. The minimization of air artifacts noted by De Reuck et al. [9] when brain sections were submerged in physiological serum would support this. Schrag et al. [7] did not comment on false negatives or provide enough information to allow for other calculations.

In keeping with previous studies, lipofibrohyalinosis and cerebral amyloid angiopathy were the dominant vascular changes associated with CMBs [12–15]. However, CMBs have been documented at the capillary level independently of the above [16]. In those with documented cerebral amyloid angiopathy, CMBs were more frequently found in the cortico-subcortical regions, as noted elsewhere [17, 18]. Microaneurysm formation has also previously been encountered in the vicinity of hemosiderin deposition [19–21]. The patient with moyamoya disease displayed disruption of the internal elastic lamina, which would support a different underlying etiology accounting for the 21.2% prevalence of CMBs in this disease population [22–24].

The notion that the presence of lacunar infarcts and white matter disease (WMD) increases a patient's risk of ICH is supported by the varying degrees of tissue rarefaction, gliosis and lacunar infarction that have been found in patients with microbleeds [12, 13, 22, 25–29]. Moreover, it seems that CMBs are often associated with a degree of surrounding tissue necrosis, which would concur with the growing literature refuting their presumed asymptomatic nature [30–35].

A 'blooming effect' was noted in two studies with contrasting findings. The discrepancy is likely a function of the different imaging parameters used. Lengthening the TE or decreasing the flip angle is known to increase the size of CMBs [6]. Accordingly, in the study by Schrag et al. [7], who found a significant 'blooming effect', they used a TE of 20 ms and flip angle of 15°, in contrast to that by Tatsumi et al. [6] (TE 17 ms and flip angle 20°), who did not find any significant 'blooming effect'. De Reuck et al. [9] observed that the 'blooming effect' on 7-tesla GRE MRI was halved (from a magnitude of 5 to 2.5) by submerging the brain sections in physiological serum. Whether the different imaging media in the above studies (water [6] vs. agarose gel [7]) influenced their respective observations is uncertain.

Unfortunately, the methodology of the literature on CMBs is generally inadequate [22], and the studies included in this review are no exception. Small sample sizes, unblinded rating and histopathological analysis of CMBs, absence of proper methodology to determine sensitivity and specificity, and the heterogeneity of tissue preparation, imaging parameters, patient demographics and level of individual case detail in these studies limit the scope of analysis and conclusions derived from our review.

However, these studies have demonstrated that the association between CMBs and pathologically proven microbleeds and surrounding vascular fragility, although strong and in keeping with previously reported studies, is not absolute. Accordingly, further histopathological studies with appropriate sample sizes and systematic methodologies are required to further characterize and validate these observations. A better understanding of the underlying pathology of CMBs could then guide the design of future research into their clinical relevance and implications.

Appendix

Search Strategy

A search of MEDLINE, Embase and the Cochrane Central Register of Controlled Trials with no date or language limitations was conducted in June 2010. Broad search terms were used as follows:

- microbleed
- microhaemorrhage
- microhemorrhage

(1 or 2 or 3).

The same search was applied to conference abstract databases from the International Stroke Conference, the European Stroke Conference and the American Academy of Neurology Annual Meeting from 2008 to 2010 to identify unpublished studies. Moreover, the references of the included trials and recent review articles were checked for additional studies.

A flow diagram of our literature search and study selection is shown in figure 1.

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