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The corresponding author had access to all data and takes responsibility for the accuracy of this manuscript. All co-authors have reviewed the final draft and approve of submission.

This manuscript was published in Cerebrovascular Diseases. This draft of the manuscript is the authors' pre-publication version and contains some information not included in the published version.

The published version can be accessed here:
https://www.karger.com/Article/Abstract/452718

Funding: there was no funding source for this study

Conflicts of interest and disclosures: None of the authors have conflicts of interest related to this data. This manuscript is not under review at any other journal. There are no redundant publications based on this dataset. All co-authors meet the ICMJE requirements for authorship.

Cerebral Microhemorrhages and Meningeal Siderosis in Infective Endocarditis

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ABSTRACT

Objective: Patients with infectious endocarditis (IE) frequently experience cerebral insults and neurological involvement in IE has been reported to herald a worse prognosis. Susceptibility-weighted imaging (SWI) is an exquisitely sensitive magnetic resonance imaging (MRI) sequence for detecting hemorrhagic processes within the brain. In this manuscript we describe a distinctive pattern of findings on SWI sequences related to IE.

Methods: All cases of definite infective endocarditis from 2009-2014 treated at an academic tertiary care hospital who underwent SWI MRI were retrospectively analyzed. The pattern of findings was compared to SWI findings in groups of subjects with either cerebral amyloid angioapthy or severe hypertension (with ten subjects in each comparison group).

Results: Sixty-six subjects with infective endocarditis were included; 94% had microhemorrhages and the average number of microhemorrhages per patient was 22. In 17% of cases, microhemorrhages were present in the absence of corresponding diffusion restriction. A direct comparison of GRE-T2* and SWI was done in ten cases; 179 microhemorrhages were detected by SWI and 65 by GRE-T2*. The majority of microhemorrhages were between 1-3 mm on SWI; many in this size range were not detected by GRE-T2*. Microhemorrhages in infective endocarditis were widely distributed, with a significant predilection for the cerebellum in a pattern distinct from that seen in hypertension or cerebral amyloid angiopathy. Small subarachnoid hemorrhages or superficial siderosis were also frequently detected, but not associated with mycotic aneurysms.

Interpretation: SWI is a sensitive diagnostic technique for detecting infectious cerebral angiopathy in subjects with infectious endocarditis producing a pattern of microhemorrhages distinct from other common microangiopathies.

INTRODUCTION

Patients with infective endocarditis often have cerebrovascular involvement and when present is associated with worse outcome. [1] Neurological involvement also complicates the management of these patients, particularly with respect to the timing of valve replacement and the safety of anticoagulation given the increased risk of intracerebral hemorrhage.[2] Classical physical examination findings in infective endocarditis include systemic microhemorrhagic events such as splinter hemorrhages and Roth's spots. More recently, petechial hemorrhage in the brain has been reported in a high proportion of patients with infective endocarditis with gradient-echo MR imaging.[3,4] There is also the suggestion in at least one study that these microhemorrhages portend a grave prognosis.[5] The advent of advanced imaging techniques, including susceptibility-weighted imaging (SWI), which is exquisitely sensitive to iron products, may enable early detection of central nervous system involvement in IE, which may have diagnostic and prognostic utility. The objective of this study is to describe the pattern of findings on brain SWI in subjects with infective endocarditis (IE).

METHODS

Case selection

This study was approved by the institutional review board of Yale-New Haven Hospital. All cases of IE at Yale-New Haven Hospital since 1 January 2009 who had brain imaging with SWI were retrospectively reviewed. Exclusion criteria were the absence of a vegetation or perivalvular abscess on echocardiography, absence of bacteremia, and MRI imaging of inadequate quality. Subjects without culture proven bacteremia were only included when cultures were drawn after antibiotics were started, and in this setting, subjects could be included if they had a documented fever and the final clinical diagnosis was definite endocarditis by the modified Duke criteria.[6]

Ten cases of severe hypertension and ten cases of cerebral amyloid angiopathy (CAA) were selected for comparison. Severe hypertension was defined as subjects with uncontrolled hypertension or requiring two or more anti-hypertensive medications for control and at least one of the following – concentric hypertrophy of the left ventricle by echocardiography or electrocardiographic criteria, chronic kidney disease attributed to hypertension, Binswanger's type dementia, lacunar stroke or small to moderate (<45ml) symptomatic hemorrhage within the basal ganglia. Cases of CAA were identified according to the modified Boston criteria.[7] These cases had either a small symptomatic lobar intracerebral and/or subarachnoid hemorrhage, cognitive impairment or brief spells of neurologic deficits associated with at least two microhemorrhages in a typical pattern for CAA. For both hypertensive and CAA cases, subjects with large intracerebral hemorrhages causing significant mass effect were excluded. None of the subjects in these comparison cohorts had a history of endocarditis, valve replacement, or ascending aortic dissection (excluded by history and echocardiography and/or CT angiography). Cases with CAA had well-controlled blood pressure and were not on more than one antihypertensive agent.

Imaging parameters and interpretation

Medical records were reviewed for age, major comorbidities, MRI findings, echocardiography results, and microbiological studies. SWI sequences were obtained for clinical indications on a 3 Tesla Siemens scanner, with an echo time of 20 milliseconds, relaxation time 27 milliseconds, field of view 182 x 256 and no interslice gap. Hypointensities less than 10 mm in largest diameter were reviewed to ensure they were not related to bone or other probable calcification artifacts, and were clearly distinct from vascular elements. Hypointensities meeting these criteria were termed microhemorrhages. Because of age-related mineralization of the lentiform nuclei and the high-probability of false-positive findings on SWI, no microhemorrhages were counted if they were located in the putamen or globus pallidus. Lesions greater than 10 mm in diameter were not considered microhemorrhages. Any area of hypointensity on SWI greater than 10 mm in length and in a serpiginous/gyriform pattern more consistent with a hemorrhage in the subarachnoid space was termed subarachnoid hemorrhage and designated symptomatic or asymptomatic. All microhemorrhages greater than 5 mm in diameter and all areas of subarachnoid hemorrhage were evaluated against vascular imaging (CT angiography, MR angiography and/or conventional angiography as available) to see if there was a corresponding aneurysm or other vascular anomaly.

Statistics

Demographic data are presented as mean and standard deviations. The significance of between group differences for demographic variables was assessed with the Z-test for two population proportions. Interrater reliability of microhemorrhage detection was assessed by having two authors rate a subset of ten MRIs and assessed for concordance

by Kappa statistic. Measured regional distributions of microhemorrhages for each group were compared to a modeled random distribution by Chi-square goodness of fit. The modeled random distribution was drawn from reported volumes of brain regions in volumetric studies of normal brain.[8-12] Because microhemorrhages in the lentiform nucleus were not counted, the volume of the lentiform nucleus was excluded from the model of the random distribution. Comparison of mean diameter of microhemorrhages in each group was done with the Student T-test. For all comparisons, alpha <0.05 was accepted as a statistically significant result.

TABLE 1: Patient characteristics

		Total	Cases with fewer than 10 MBs	Cases with 10 or more MBs	P value
Number of cases		66	25	41	
Percent male		61%	56%	64%	n.s.
Age +/- SD		56.8+/- 16.8	58.6+/- 18.6	53.9+/- 17.5	n.s.
Survival at 1 year		77%	84%	73%	n.s.
Size of vegetation (cm) +/- SD		1.1 +/- 0.6	1.2 +/- 0.7	1.1 +/- 0.6	n.s.
% on antiplatelet / anticoagulation			28% / 20%	18% / 21%	n.s.
Comorbidities					
	Prior episode of endocarditis	17%	12%	21%	n.s.
	Pre-existing structural heart disease	38%	32%	41%	n.s.
	Prosthetic valve	39%	16%	53%	**0.004**
	End-stage renal disease	27%	32%	23%	n.s.
	HIV	8%	4%	10%	n.s.
	Pharmacologic immunosuppression	14%	20%	10%	n.s.
	Intravenous drug abuse	17%	8%	23%	0.14
	Malignancy	13%	4%	18%	0.11
	Diabetes	25%	28%	23%	n.s.
	Renal calculi, ureteral stent or chronic urinary catheter	8%	8%	8%	n.s.
	Chronic infection (excluding HIV)	16%	20%	13%	n.s.
Infectious agent					
	Staphylococcus	42%	40%	44%	n.s.
	Streptococcus	20%	32%	13%	0.05
	Enterococcus	12%	12%	12%	n.s.
	Gram-negative species	5%	0%	7%	n.s.
	Fungal	6%	0%	10%	0.11
	Multi-organismal	5%	4%	5%	n.s.

RESULTS

Subject characteristics

Ninety-five subjects were identified meeting inclusion criteria for this study. Twenty-nine were censured prior to analysis for insufficient imaging quality (MRI or echocardiography), absence of vegetation on echocardiography or failure to meet criteria for definitive IE. The remaining 66 cases were analyzed. The subjects were 61% male with a mean age of 56.8 +/- 16.8 years. Risk factors for IE and causative organisms were typical for this population and are shown in detail in table 1.

Microhemorrhages

Images were interpreted by two trained observers (MS, BMG) with oversight by an experienced neuroradiologist (AM). Microhemorrhages were detected with good interrater reliability, kappa 0.88, 95% confidence interval 0.81-0.94. Microhemorrhages were detected in 94% of the cases in this series (all but 4 cases); the mean number of microhemorrhages was 21.5 per case, and 10 or more were detected in 62%. Microhemorrhages were broadly distributed

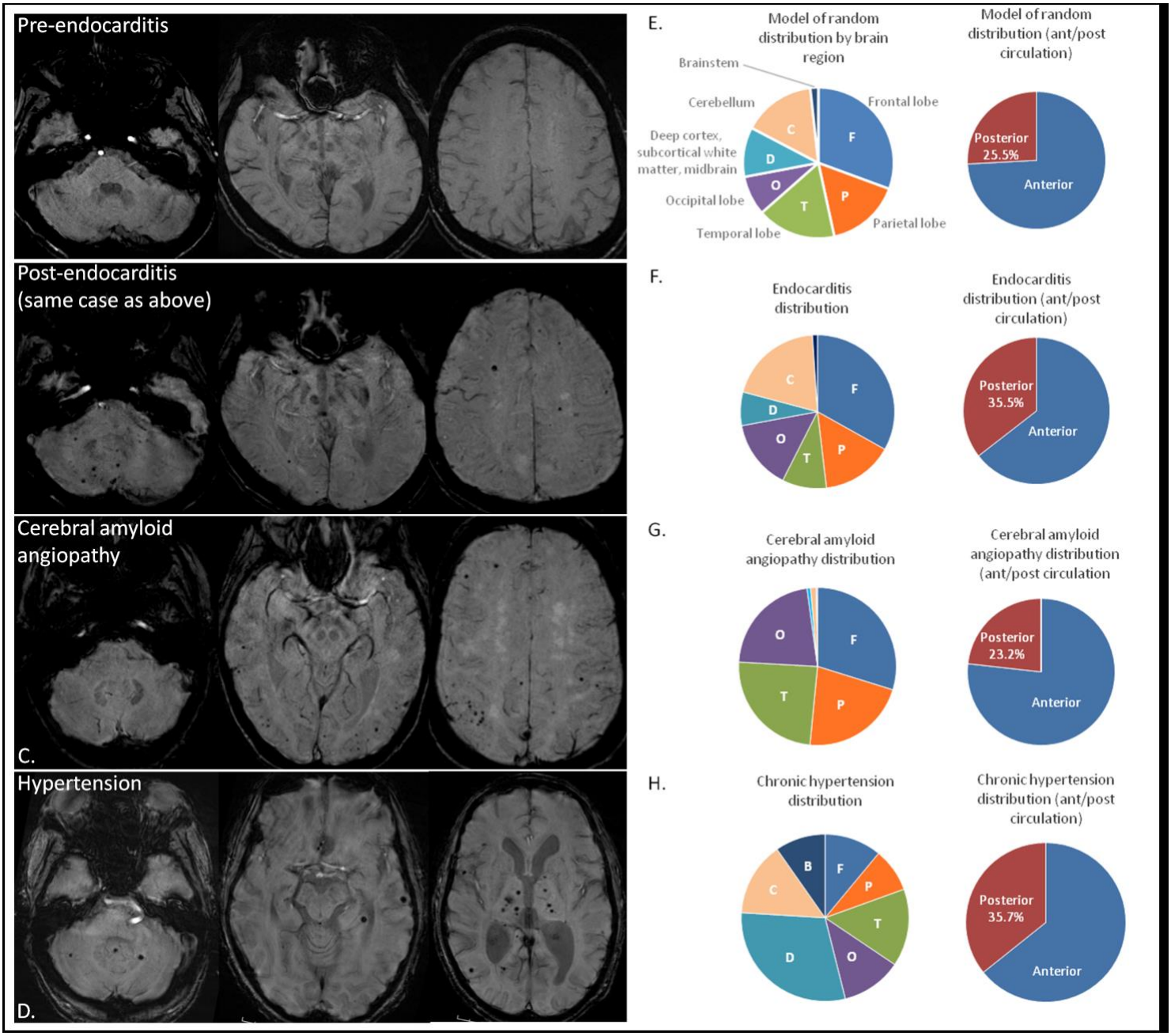

Figure 1. A. MRI from a patient prior to an episode of infectious endocarditis does not demonstrate microhemorrhages. B. Matched images from the same patient after the onset of infectious endocarditis demonstrates multiple microhemmorhages and an area of cortical superficial siderosis in the right frontal lobe. C.Typical MRI from a patient with cerebral amyloid angiopathy demonstrates the cortical/lobar pattern of microhemorrhages which rarely involves the cerebellum or deeper structures. D. Typical MRI from a patient with severe chronic hypertension demonstrates widely distributed microhemorrhages with a preference for the basal ganglia and frequently involving the cerebellum. E.A model of a predicted random distribution of microhemorrhages in the brain is shown in the first row for comparison. F. The distribution of microhemorrhages in infective endocarditis involves essentially every brain region but has a significant preference for the posterior circulation, particularly the cerebellum when compared to a random distribution. G. The distribution of microhemorrhages in cerebral amyloid angiopathy is shown to spare the basal ganglia and cerebellum with preferential involvement of cortical areas. H. The distribution of microhemorrhages in patients with severe chronic hypertension preferentially involves in the basal ganglia, but does not spare cortical areas or the cerebellum.

with a significant preference for the posterior circulation, particularly the cerebellum when compared to a statistical model of a random distribution (p-value of <0.0001, figure 1).

The distribution of microhemorrhages in the severe hypertension and severe CAA groups were significantly different from the distribution in IE, p<0.0001. In the 10 subjects with severe hypertension, 154 microhemorrhages were detected and they preferentially involved the deep brain structures and the cerebellum as has been previously reported.[13] In the 10 subjects with severe CAA, 422 microhemorrhages were detected and there was a strong preference for a lobar distribution, again consistent with previous reports.[14]

In IE, microhemorrhages were often not round and the majority of microhemorrhages were between 1-3 mm in diameter (Fig 2). The size range of microhemorrhages was comparable to subjects with CAA, but significantly smaller than microhemorrhages associated with severe hypertension, p<0.0001. Sixty-two percent of the subjects with IE had at least one microhemorrhage greater than 5 mm in diameter. In the cases evaluated with contrast enhanced MRI, 8 of 24 microhemorrhages between 5 and 10mm in diameter had associated contrast enhancement. 17% of subjects had microhemorrhages in the absence of any abnormality on diffusion weighted or T2 weighted sequences. Ten cases were assessed with both SWI and GRE-T2*. In these cases, more microhemorrhages were detected on SWI than GRE-T2* (179 versus 65), and in one case microhemorrhages were seen on SWI but none were present in the GRE-T2*. GRE-T2* was less sensitive for the detection of small microhemorrhages in the 0.5 to 3 mm diameter range (figure 2). In five subjects with follow-up MRI 1 year after the initial imaging, all but 7% of microhemorrhages were still visualized. The involvement of a prosthetic valve was strongly predictive of a higher number of microhemorrhages, p=0.004. Streptococcal infections were weakly associated with lower microhemorrhage burden, p=0.05.

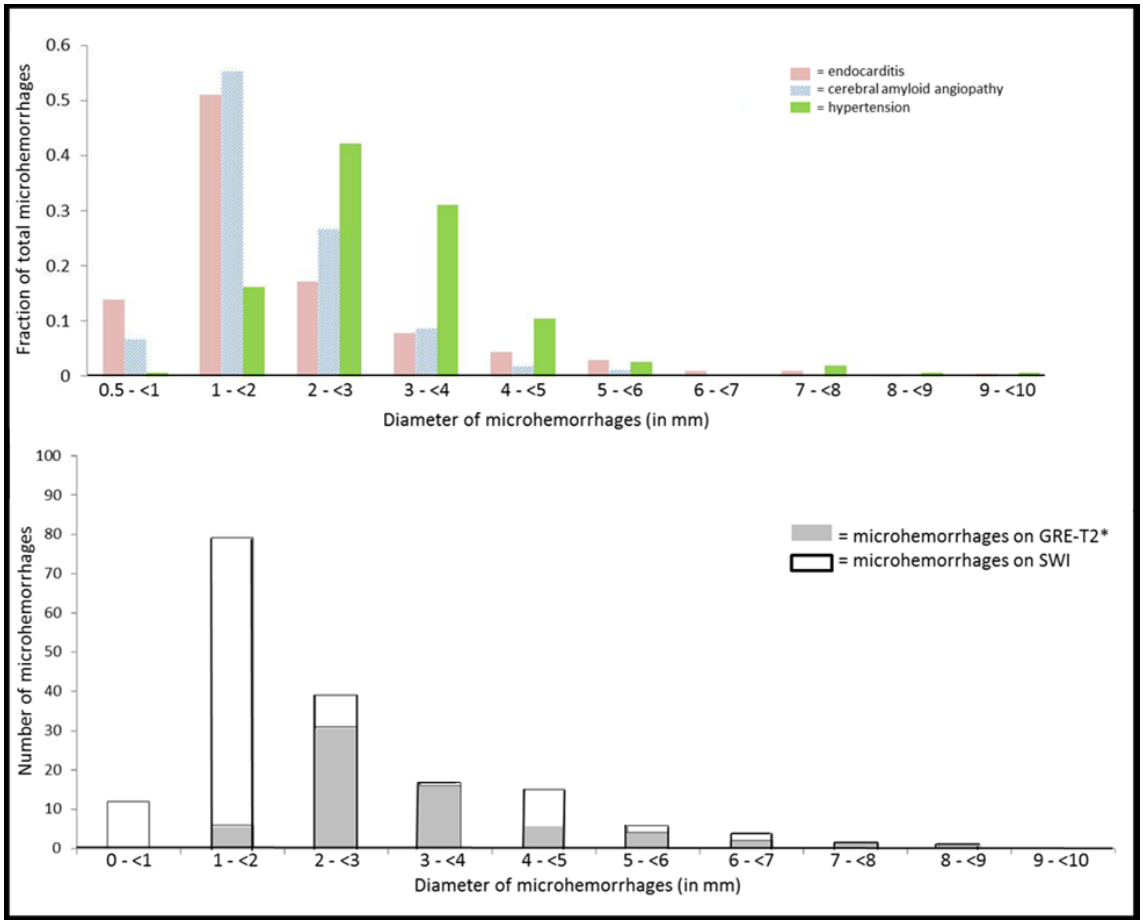

Figure 2: Microhemorrhages in cerebral amyloid angiopathy and infective endocarditis are about the same size, while microhemorrhages in severe hypertension are significantly larger (p<0.0001). The sensitivity of GRE-T2* for the detection of microhemorrhages is significantly lower than SWI, particularly for microhemorrhages between 0.5 and 2mm in diameter in infectious endocarditis.

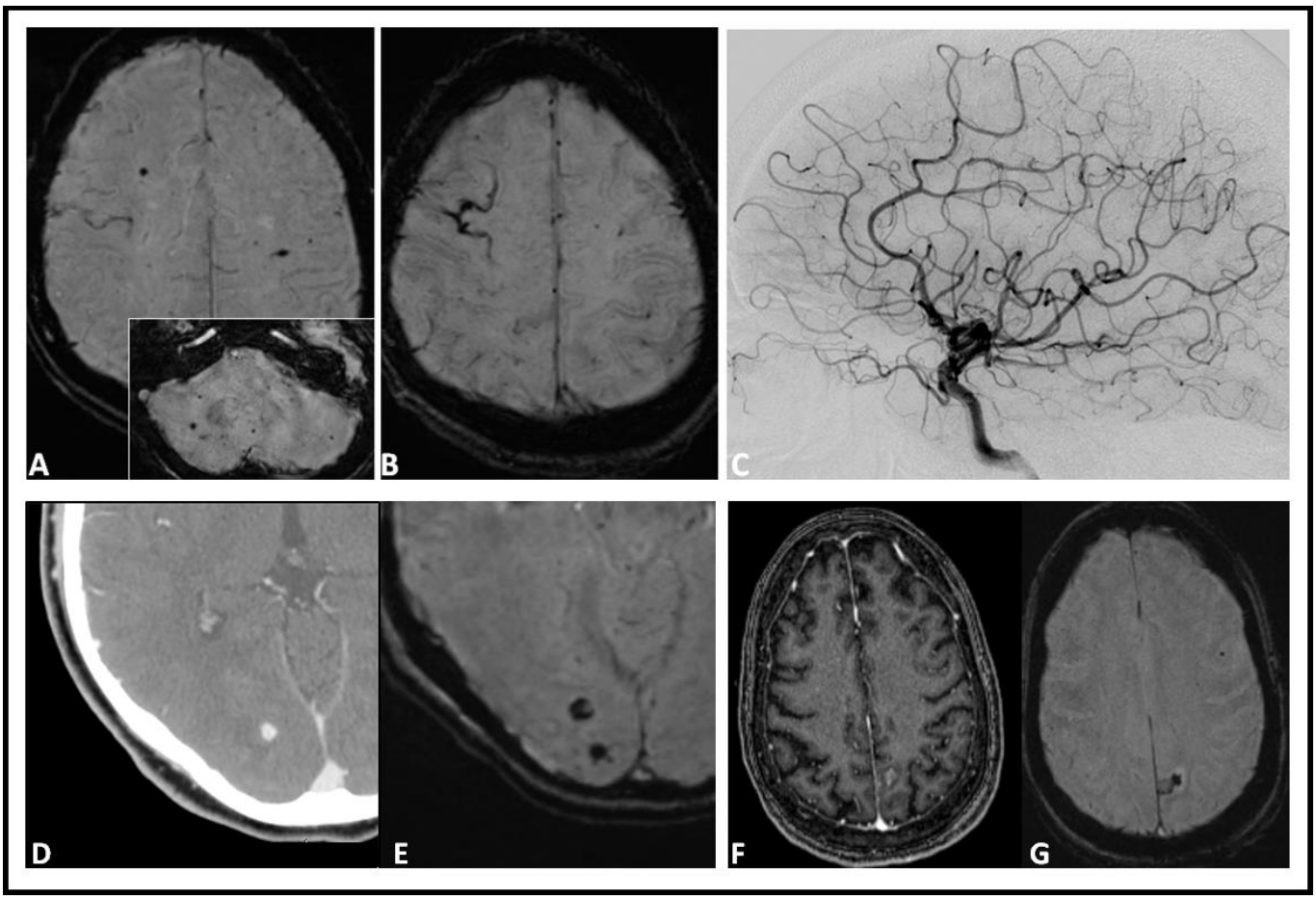

Figure 3: Mycotic aneurysms are rarely detected, and convexity subarachnoid hemorrhage or superficial siderosis are not closely associated with mycotic aneurysms. (A-B) A typical area of superficial siderosis in the right frontal lobe in a patient with typical SWI features of infective endocarditis (cerebellum in inset); (C) conventional cerebral angiography of the right internal carotid artery did not reveal an aneurysm or vasculopathy. D,E One mycotic aneurysm was detected which did have an SWI correlate; we found no other similar examples. F,G Several areas of superficial siderosis were associated with focal enhancement on post-gadolinium contrast images.

Superficial siderosis and mycotic aneurysms

Superficial siderosis was present in 45% of subjects in this series. The majority of areas of superficial siderosis were in the frontal and parietal lobes, often cranially near the vertex (see figure 3a,b,c). Seventy-six percent of subjects in this series had concurrent imaging with CT angiography, MR angiography or conventional angiography (36%, 48% and 9% respectivelyand 17% had more than one angiogram modality) for screening of mycotic aneurysms. Only one hypointensity was found to correlate with mycotic aneurysm on angiography (figure 3d,e). Four additional mycotic aneurysms were detected on CT angiography and/or conventional angiography in two subjects; these were not appreciated on SWI. None of the 28 subjects with superficial siderosis had evidence of an associated mycotic aneurysm (22 of the 28 were evaluated with some angiographic technique). Four subjects had areas of superficial siderosis associated with foci of contrast enhancement on post-gadolinium T1-weighted imaging. This imaging finding has previously been interpreted as a thrombosed aneurysm. However in our series, this imaging finding was associated with leptomeningeal enhancement, and may therefore reflect meningitis/cerebritis, abscess or venulitis rather than a thrombosed aneurysm. [15]

DISCUSSION

Symptomatic intracerebral hemorrhage occurs in about 27% of cases of infective endocarditis in the intensive care unit setting, and its occurrence is associated with a very poor prognosis.[1] Limited data is presently available describing the prevalence, distribution and clinical and vascular correlates of microhemorrhages in the brain in infectious endocarditis. Neuroimaging of cerebral microhemorrhages in IE was first reported in a case report by Subramaniam and colleagues in 2006.[16] Klein and colleagues reported the first large series using gradient-echo T2* and found a prevalence of 57% at

1.5 Tesla field strength.[3] A subsequent study reported on a small cohort of subjects with gradient echo T2* imaging, and found that the presence of microhemorrhages correlated with impending symptomatic hemorrhage in nearly 30% of subjects within 3 months.[5] Another study found that obtaining MRI with an iron-sensitive technique altered clinical management in a meaningful portion of cases.[17] Increasing use of higher field strength magnets and susceptibility weighted imaging have greatly increased the sensitivity and accuracy of detection of cerebral microbleeds. SWI is a three dimensional high resolution gradient sequence and combines both magnitude and phase information. It is four times more sensitive than conventional T2* imaging for detection of hemorrhage and is reliable for detection of blood degradation products over a long period of time.[18,19] The current study was conducted at 3Tesla field strength using SWI and found that cerebral microhemorrhages occur in 94% of patients with IE, making it a sensitive marker of central nervous system (CNS) involvement in this condition.

The differential etiology of cerebral microhemorrhages is broad and includes cerebral amyloid angiopathy, hypertension, Alzheimer's disease, vascular dementia, and genetic microvascular disease.[20] The pattern of neuroimaging findings on SWI in IE is characteristic. In IE, microhemorrhages are common and are widely distributed, but have a preference for the posterior circulation, particularly the cerebellum. Most microhemorrhages are small measuring 1-3 mm in diameter on SWI, but one or more larger microhemorrhages between 5-10 mm occur in most patients. These features distinguish microhemorrhages related to IE from hypertension or CAA. In CAA, microhemorrhages typically form in lobar areas, while the basal ganglia and cerebellum are rarely involved. Microhemorrhages between 5 and 10 mm in diameter are rare in CAA. In severe hypertension, deep grey structures including basal ganglia are preferentially affected, and microhemorrhage-associated susceptibility artifacts are typically larger in diameter (about 3 mm on the average). In both of these conditions, microhemorrhages tend to be round, while irregularly shaped hemorrhages are more common in infectious endocarditis.

The mechanism of microhemorrhage in the context of infectious endocarditis is likely to be cardioembolic in at least a portion of the lesions (analogous to Roth's spots in the retina). However, microhemorrhages were frequently observed in subjects without evidence of concurrent ischemic injury on diffusion-weighted imaging. Mycotic aneurysms do not account for the overwhelming majority of hypointensities on SWI. The fact that the rate of stroke remains 12.9 to 14.0 % even after successful antibiotic treatment and most of these events occur in the first week also raises the possibility of non-embolic etiology.[21,22]. An alternative explanation for the mechanism of microhemorrhage is related to the toxic effects of the immunological reaction to severe chronic infection which may disrupt the cerebral microvasculature. This has been modeled in mice subjected to repeated intraperitoneal injection of lipopolysaccharide which induced extensive cerebral microbleeding with early involvement of the cerebellum, a pattern reminiscent of the pattern observed in IE.[23,24] In our series, gram-negative infections were uncommon, but all three cases had a high number of microhemorrhages. The cerebral microvasculature may be disrupted by injury secondary to complement activation and immune complex formation as has been observed in other systemic effects of IE.[25] Additionally, intense systemic activation of matrix metallopreteinases has been documented in IE.[26] Damage to the cerebral microvasculature due to local activation of matrix metalloproetinases and the late complement cascade are the major mechanisms of microhemorrhage in CAA —the mechanism of microhemorrhage in IE may be due to systemic activation of these same processes.[27-30] This type of microvasculopathy has been proposed to contribute to the early "non-specific" encephalopathy of infective endocarditis, although this remains to be robustly verified.[31,32]

The retrospective nature of this study is a major limitation – most patients underwent MR imaging to evaluate symptoms while a minority were scanned for surveillance which may exaggerate the rate of brain involvement compared to a prospective screening cohort. This study was also not designed or powered to assess clinical outcomes. The six month mortality rate of 25% in this cohort is similar to prior reports [33], but it is not yet clear to what degree microhemorrhagic findings in the brain affect the natural history of this disease or whether it should alter management. Certainly SWI is promising as a sensitive tool in the diagnosis of IE related cerebral microbleeds. Additionally, the very high rate of microhemorrhage in this cohort raises questions regarding the safety of acute anticoagulation which may delay the timing of valve replacement surgery. In cases of IE complicated by peripheral embolic disease or heart failure, early surgical intervention is reported to improve outcomes.[34] However, embolic ischemic and hemorrhagic injury to the brain may be associated with a high rate of hemorrhagic transformation which makes the use of anti-coagulation in the acute phase particularly dangerous, thus complicating the decision to proceed with surgical implantation of a prosthetic heart valve. This scenario is fairly common and unfortunately there is no solid evidence to guide clinical decision-making. These questions will need to be evaluated in a prospective study, preferably in the context of a randomized clinical trial. However, before this is done, the mechanism(s) underlying this hemorrhage-prone state need to be clearly understood.

Recent population based studies have shown that patients with IE had a 2.4-times higher risk of developing long term hemorrhagic stroke than age matched controls.[35] Reliable markers of active infectious cerebral angiopathy which predict the presence of a hemorrhage-prone state would be helpful to guide the timing of surgical intervention in individual patients and determine prognosis.

Author contributions

AM and JS prepared the IRB application, assisted in study design, data collection and data interpretation; BMG participated in interpreting images and statistical analysis of the data; TSY, SYC and CM assisted in study design and correlated SWI data to vascular imaging; DMG was involved in study design and critically reviewed the data analysis; MS conceived the study, collected primary data, performed statistical analysis and wrote the manuscript. All authors critically revised the manuscript for meaningful intellectual content.

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