

Cerebral Microbleeds in Stroke

What are cerebral microbleeds?

Over the last decade, gradient echo MRI has disclosed small, dot-like low signal areas in patients with haemorrhagic and ischaemic stroke, hypertension, and in healthy elderly subjects.^{1,2,3,4} These 'microbleeds' (or 'microhaemorrhages') are tiny focal collections of blood breakdown products adjacent to histologically abnormal small vessels,^{5,6} resulting from blood leakage through the fragile vessel wall. Microbleeds probably persist for many years, making them a potentially unique marker for an individual's lifetime history of bleeding related to small vessel pathology.

Imaging method

Gradient-echo (also termed T2*-weighted) MRI is exquisitely sensitive to blood breakdown products (including haemosiderin, deoxyhaemoglobin and ferritin) which are paramagnetic and cause local dephasing of the MR signal ('susceptibility'). Cerebral microbleeds are thus well seen as small, round, dark dots of 2-5mm diameter (Figure 1), though the actual physical size of microbleeds is likely to be less than a millimetre. Care must be taken to distinguish microbleeds from blood vessels (in the subarachnoid space) or calcification of the basal ganglia (which is often symmetrical and is easily seen on CT scans).

What causes cerebral microbleeds?

Microbleeds are associated with lacunar infarcts and clinical syndromes, and with white matter lesions (including the confluent changes of leukoaraiosis),^{3,7} suggesting that they result from small vessel damage. Their usual distribution, in the basal ganglia (including the putamen and thalamus), and the pons, in the territory of the small, deep perforating arteries, supports this idea. Moreover, in most studies microbleeds are more common in patients with hypertension.^{1,8,9,10} and left ventricular hypertrophy on echocardiography correlates with their severity.¹¹ In a smaller group of patients (generally elderly, presenting with lobar haemorrhage) microbleeds are found at the cortico-subcortical junction in the territory of small and medium-sized leptomeningeal and cortical vessels; in this distri-

bution, and in the appropriate clinical context, they are probably caused by cerebral amyloid angiopathy rather than hypertensive small vessel damage, though the conditions may co-exist.⁴

Recent experimental and human genetic studies of familial small vessel disease showed that mutations in the collagen IV gene predispose to small vessel damage and microbleeds,¹² but further studies are urgently needed to clarify the genetic contribution in the much more common sporadic patients. Microbleeds may be a useful intermediate phenotype for increasing the power of studies to detect genetic effects in small vessel stroke. One study has shown an independent inverse relationship between microbleed number and serum cholesterol, but a causal link is not established.⁹

Who gets cerebral microbleeds - and what is their significance?

(1) Healthy individuals with no history of stroke

Microbleeds are found in about 5% of the normal population in their fifth to eighth decades, increasing in prevalence with age to about 7-8% of patients over 70 having MRI for non-stroke indications.^{7,13,14} The clinical significance of cerebral microbleeds in an otherwise healthy individual is unknown, but they may predict an increased future cerebrovascular risk.

(2) Primary Intracerebral haemorrhage

Primary intracerebral haemorrhage (PICH) accounts for about 20% of all strokes, and is usually caused by rupture of a small or medium-sized arterial wall (trauma, arteriovenous malformations or intracranial aneurysms are conventionally excluded from this diagnostic group). Cerebral microbleeds are found in between 54% and 71% of PICH,^{7,10,15,16,17,18} and are especially common in Asian populations, which to date have been the most extensively studied.¹⁹

Cerebral amyloid angiopathy (CAA) is less common (though probably under-recognized) and causes recurrent, often non-disabling, PICH in a 'lobar' distribution, especially in elderly patients. CAA is due to amyloid deposition in small to medium leptomeningeal



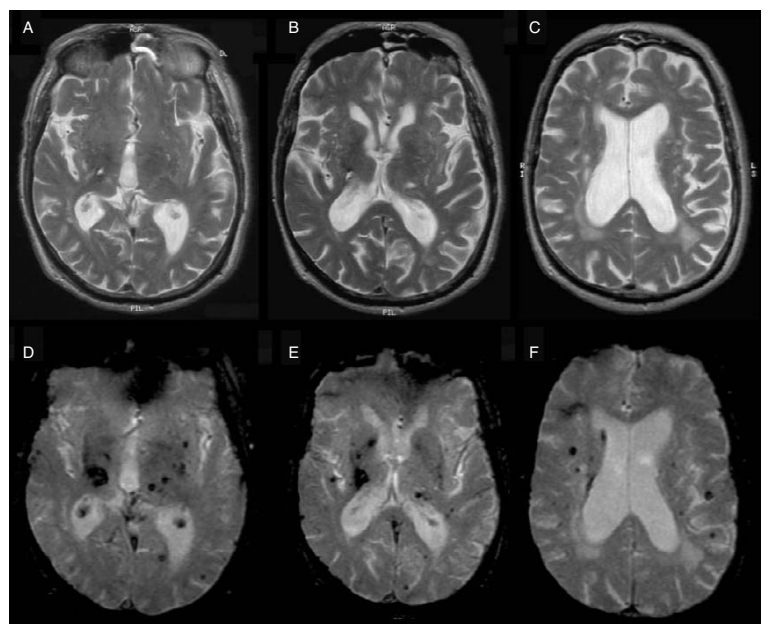
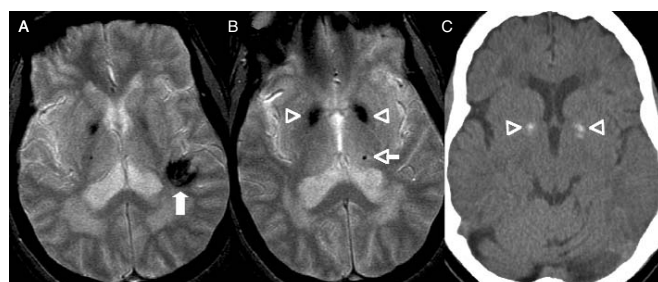
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Figure 1 (below): (a) and (b) are axial T2*-weighted gradient-echo MR images; (c) is an axial CT scan from a 64-year-old woman who presented with sudden left sided sensory disturbance and mild weakness. She was taking warfarin for atrial fibrillation. The haematoma is located in the right temporo-parietal region (large white arrow, a). Note the microbleed (small, dark dot-like lesion, arrowed, b) in the right thalamus. Basal ganglia calcification is also present on the T2* MRI and confirmed on the CT scan (arrowheads, b and c).

Figure 2 (right): Standard axial T2-weighted images (a to c) and Gradient-echo MRI (d to f) of a patient who continued to experience cerebrovascular events despite increasingly aggressive antithrombotic treatment. When the antithrombotic therapy was reduced in intensity the frequency of events also reduced. (Figure kindly provided by Dr R Jäger, Institute of Neurology).



and cortical vessels making them fragile and prone to bleeding. Greenberg²⁰ reported microbleeds in 80% of elderly patients with lobar haemorrhage compatible with presumed cerebral amyloid angiopathy.

The location of cerebral microbleeds may help to determine the underlying cause of intracerebral haemorrhage. An exclusively cortico-subcortical distribution suggests amyloid angiopathy, whilst deeper microbleeds in the basal ganglia, brainstem and cerebellum suggest hypertensive small vessel disease. Testing this hypothesis will be challenging, since the distribution of haemorrhages on MRI forms part of some current diagnostic criteria for amyloid angiopathy. Furthermore, hypertension and CAA may co-exist, especially in an elderly population. In practice, finding microbleeds in a patient presenting with intracerebral haemorrhage suggests a diffuse bleeding-prone angiopathy rather than an arteriovenous malformation or tumour. The probability of hypertensive arteriopathy versus amyloid angiopathy will depend on the clinical context, location of the symptomatic haemorrhage and microbleed distribution. Finding microbleeds and combining the information with other clinical and imaging data could therefore potentially avoid the need for invasive angiography in some patients, but this approach remains to be tested in clinical practice.

Limited data suggest that microbleed number may predict future bleeding risk after symptomatic intracranial haemorrhage.²¹ Microbleeds are also associated with a larger volume of intracerebral haemorrhage.²²

(3) Ischaemic stroke and antithrombotic treatments

Microbleeds are found in between 18% and 65% of patients with ischaemic stroke.^{3,7,9,23,24} The wide variation reflects study population differences (hospital versus community; different proportions of stroke subtypes; and different demographic groups). Microbleeds are consistently more common in Asian patients and those with lacunar infarction compared with atherothrombotic or cardioembolic ischaemic stroke.

It was suggested that microbleeds may predict the risk of haemorrhagic transformation after acute cerebral infarction,²⁵ particularly after thrombolysis. However, a large multi-centre study found no significant difference in the rate of symptomatic intracranial haemorrhage in those with microbleeds compared to those without (8.3% in the microbleed group compared with 7.5% in the non-microbleed group).²⁶

There have been few long-term prospective studies of patients with microbleeds in ischaemic stroke, but the limited available data suggest that microbleeds confer an increased risk of both haemorrhagic²³ and ischaemic events.²⁷

Patients with ischaemic stroke are often treated with antithrombotic agents, and antithrombotic-associated intracerebral haemorrhage, the most feared complication, accounts for up to 14% of all PICH. Although leukoaraiosis and lacunar infarcts on CT scanning are associated with increased haemorrhagic risk,²⁸ the risk remains difficult to predict. Cross-sectional retrospective data reported that patients with aspirin-related intracerebral haemorrhage more often had microbleeds than matched patients taking aspirin without haemorrhage (90% vs 30% microbleed prevalence)²⁹ but whether microbleeds predict future bleeding risk urgently needs to be tested prospectively in a larger cohort of patients, including those on anticoagulants.

Microbleeds may help to guide antithrombotic treatments in patients with recurrent stroke or TIA events despite treatment. Figure 2 shows gradient-echo MRI in a patient who continued to experience recurrent transient focal neurological attacks despite increasingly aggressive antithrombotic treatment, culminating in anticoagulation. The finding of numerous microbleeds led to the antithrombotic treatment being discontinued, and the 'TIA's stopped. It is possible that some or all of the recurrent events could have been related to the formation of new microbleeds, but this hypothesis cannot be confirmed without longitudinal imaging.

Few studies have investigated microbleeds in patients with TIA, but one study found microbleeds in only 2% of TIA patients compared with 24% of ischaemic stroke patients matched for demographic and vascular risk factors and for MRI white matter abnormalities.³⁰

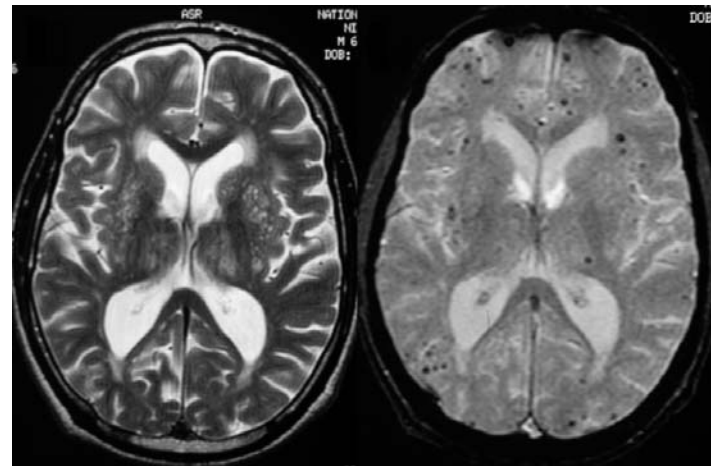


Figure 3: T2-weighted (a) and gradient-echo MRI (b) of a patient with frontal-executive dysfunction. Note the numerous microbleeds present, particularly in the frontal regions on the gradient-echo image (right hand panel), which are not visible on the T2-weighted image (left hand panel). The distribution is suggestive of cerebral amyloid angiopathy. Reproduced with permission from reference 33.

Table 1: prevalence of microbleeds in different groups of subjects / patients

Disease	Proportion of patients with microbleeds (%)	Selected references
Normal elderly	4.5-8.5	7,13,14
Ischaemic stroke	18-65	3,7,9,23,24
TIA	2	30
PICH	54-71	7,10,15,16,17,18
Cerebral amyloid angiopathy	80	20
CADASIL	31-69	31
Moya Moya	15-44	32

Table 2: aspects of stroke medicine where microbleeds may be clinically important

• Guiding decisions about antithrombotic treatments and risk of intracranial haemorrhage
• Investigating the underlying cause of primary intracerebral haemorrhage
• Prognostic information after ischaemic or haemorrhagic stroke
• Investigating patients with unexplained cognitive disturbance, especially if they have vascular risk factors
• Screening and monitoring patients in clinical trials of antithrombotic or antihypertensive agents
• Intermediate phenotype for stroke genetic studies in small vessel disease

Microbleeds therefore may be markers for a more severe small vessel vasculopathy than is revealed on conventional MRI, to the extent that there is an increased risk of ischaemic stroke. Furthermore, antithrombotics may be less hazardous in patients with transient syndromes than those with stroke.

Microbleeds have been detected in up to 69% of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a single-gene disorder of small vessels due to a mutation in the Notch-3 gene, and seem to occur largely outside areas of ischaemia.³¹ Asymptomatic microbleeds were reported in 28% of patients with Moya Moya disease at 1.5T field strength, increasing to 44% at 3T.³²

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Do microbleeds cause symptoms?

Microbleeds have been considered to be asymptomatic,^{3,4,7,10} but recent studies suggest that they may not be as clinically silent as was first thought. We investigated cognitive function in patients with cerebral microbleeds compared to a non-microbleed control group matched for age, white matter changes on MR, stroke subtype and associated large-vessel stroke.³³ Executive dysfunction was twice as common in microbleed patients (60% vs 30%) and was related to microbleed burden in the frontal lobes and basal ganglia, suggesting that cognitive impairment could result from disruption of strategic frontal-basal ganglia circuits. These findings may

assist the assessment of stroke patients with cognitive impairment, and influence the use of antihypertensive and antiplatelet treatments. Figure 3 shows gradient echo and T2-weighted MRI in a patient with frontal-executive dysfunction.

Clinical experience suggests that small haemorrhages can cause distinct stroke syndromes: indeed, a recent case report describes a patient with abrupt onset of lateral gaze disturbance due to a cerebral microbleed in the medial lemniscus at the mid-pontine level.³⁴ Microbleeds may also cause partial seizures secondary to irritation of adjacent cerebral cortex, which respond to anticonvulsants.³⁵

Conclusion

Microbleeds are a recently described imaging finding in patients with stroke, related to pathological damage to small vessels. Although knowledge has increased rapidly in the decade since their first description, many important questions remain. Perhaps the most urgent of these is whether microbleed imaging can help predict stroke patients' haemorrhagic risk when treated with antithrombotic agents. The general significance of microbleeds for haemorrhagic and ischaemic stroke risk, and for vascular cognitive impairment, also need to be further clarified. Clear imaging criteria for microbleeds need to be developed to allow multi-centre prospective studies to answer these questions.

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