Point of view

Cerebral microbleeds and stroke: more questions than answers

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Abstract

With the widespread availability of MRI scanning, cerebral microbleeds (CMBs) are being increasingly recognised in patients with stroke and in healthy individuals. As CMBs are commonly viewed as markers of increased risk of intracerebral haemorrhage (ICH), there are concerns regarding the use of antithrombotic agents (antiplatelets, and especially anticoagulants) in the presence of CMBs, even in patients at high risk of ischaemic events. The use of antiplatelet or anticoagulant therapy in the presence of CMBs, balancing the risk of recurrent ischaemic stroke against the risk of possible intracranial bleeding, is one of the most contentious contemporary issues in stroke medicine.

Key words: cerebral microbleeds; stroke; intracerebral haemorrhage; ischaemic stroke; antiplatelets; anticoagulants

What are cerebral microbleeds?

CMBs are a radiological biomarker of cerebral small vessel disease. They are seen on blood-sensitive MRI sequences such as T2*-weighted gradient-recalled echo (T2*-GRE) or susceptibility-weighted imaging (SWI)[1,2,3,4,5,6]. They are small (usually <5 mm in diameter), rounded or oval lesions of low signal intensity in the brain parenchyma[1,2,3,4,7,8]. CMBs represent haemosiderin deposits contained within macrophages in the microvascular perivascular spaces on histopathological examinations[1,2,3,4,9], and develop as a result of leakage of red blood cells secondary to rupture of the walls of small arteries, arterioles or capillaries[1,2,10]. Whether the rupture of a small vessel results in a microbleed or a larger macrobleed is believed to depend on different vasculopathic features and environmental exposure[5,7]. Two distinct patterns of microangiopathy are noted on histopathological testing in the blood vessels located near CMBs: lipohyalinosis and cerebral amyloid angiopathy (CAA). The pattern of microangiopathy appears to determine the pattern of anatomical distribution of CMBs; lobar CMBs are associated with CAA in superficial perforating arteries, deep subcortical or infratentorial CMBs result from arteriosclerosis or lipohyalinosis related to hypertensive arteriopathy of deep perforating arteries, and a mixed distribution in both locations is seen with a mixed pattern of microangiopathy[2,3,5,6,9,11].

CMBs: What do they mean?

Prevalence of CMBs is highly variable, depending on the demographic and clinical characteristics of the population studied and the MRI criteria of assessment. They are reported in 3-27% of the general population, and 6-80% of patients with vascular risk factors or vascular disease[2]. In population studies, CMBs were associated with older age, hypertension, diabetes, smoking and previous stroke[2,3,6,12].

CMBs and stroke

CMBs are more prevalent in patients with stroke, and in patients with ICH than ischaemic stroke[1,2]. In a systematic review, CMBs were seen in 5% of healthy adults compared to 45% of patients with any stroke, 34% with ischaemic stroke and 60% with ICH[12].

CMBs predict increased stroke risk. In a meta-analysis, CMBs increased the risk of ischaemic stroke (odds ratio [OR]: 2.14), ICH (OR 4.65) and death (hazard ratio: 1.36)[13]. CMBs are a marker of small vessel disease. They are more frequent in patients with lacunar strokes than cortical strokes[1,2,14,15,16], and in those with a higher burden of white matter lesions (WMLs) in periventricular or deep white matter regions[1,12,14]. CMBs are reported to be twice as frequent in patients with lacunar strokes (26%) than cortical strokes (13%)[1].

CMBs are commoner among patients with recurrent strokes than first-ever strokes[12,17]. In pooled data from 54 studies, CMBs were seen in 23% with first-ever ischaemic stroke and 52% with first-ever ICH, compared to 44% with recurrent ischaemic stroke and 83% with recurrent ICH[12]. The risk of stroke recurrence appears to be greater with lobar CMBs[11,13,14], and in the presence of ≥5 CMBs[2,16,18].

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In patients with atrial fibrillation (AF), CMBs are more prevalent[19,20,21], and are associated with ischaemic stroke[19,20] and asymptomatic cerebral infarction[21]. They are reported in 30-56% of patients with AF and ischaemic stroke[7,19,20,22]. Prior antiplatelet therapy is independently associated with the presence of CMBs in patients with AF[20]. CMBs are also related to prior anticoagulation with warfarin in patients with AF, but not with non-vitamin K antagonist oral anticoagulants (NOACs)[8].

CMBs and intracerebral haemorrhage

CMBs increase the risk of ICH, particularly in patients with multiple lobar CMBs (which indicates probable underlying CAA). In a meta-analysis of data from 10 studies involving ICH survivors, a consistent association between CMB presence at baseline and risk of future ICH recurrence was seen. The risk of recurrent ICH varied with the distribution and burden of CMBs, and the underlying microangiopathy[7]. In presumed CAA-related ICH (based on a lobar distribution of ICH), the risk of recurrent ICH was 7-fold higher compared to CAA-unrelated ICH; the risk was higher in those with CMBs (28.7%) compared to those without (11.3%), and in those with a higher CMB burden. Even in CAA-unrelated ICH, the risk of recurrent ICH was higher in those with CMBs (4.6%) compared to those without (1.2%), but only the presence of more than 10 CMBs was associated with an increased risk. The presence of a single CMB did not increase the risk of recurrent ICH[7].

CMBs and ischaemic stroke

In patients with ischaemic stroke, CMBs increase the risk of both ischaemic and haemorrhagic stroke recurrence. In a meta-analysis of ten prospective cohorts with ischaemic stroke or TIA, the presence of CMBs was associated with an increased risk of recurrent stroke (OR 2.25), and the risk was greater for recurrent ICH (OR 8.52) than for recurrent ischaemic stroke (OR 1.55)[11]. Pooled analysis of individual patient data from 38 cohort studies in the Microbleeds International Collaborative Network showed that in patients with previous ischaemic stroke or TIA, the presence of CMBs on baseline neuroimaging was associated with increased risk of both ischaemic stroke and ICH, and the risk of ICH was higher than that of ischaemic stroke. The adjusted hazard ratio (comparing patients with CMBs vs. no CMBs) was 1.35 for any stroke, 2.45 for ICH and 1.23 for ischaemic stroke. The CMB burden correlated with the comparative risks of ICH and ischaemic stroke, with the risk of ICH 5 times higher than the risk of ischaemic stroke in the presence of ≥10 CMBs, and 8 times higher with ≥20 CMBs[10]. However, the absolute rate of ischaemic stroke consistently exceeded that of ICH, irrespective of age, CMB anatomical distribution, CMB burden, antithrombotic treatment and a diagnosis of probable cerebral amyloid angiopathy[10]. Similarly, the presence of CMBs was associated with a higher risk of developing new ischaemic strokes than of ICH in a European cohort of patients with ischaemic stroke or TIA[14].

CMBs and antithrombotic therapy

Antiplatelet treatment, and to a greater extent anticoagulant treatment, increase the risk of ICH in patients with CMBs[2]. In two large prospective cohorts, patients with a high CMB burden and on antiplatelet therapy following ischaemic stroke or TIA had increased risk of both ischaemic and haemorrhagic stroke [16]. In a prospective observational study of patients on anticoagulation therapy for AF with ischaemic stroke or TIA (CROMIS-2), the presence of CMBs at baseline was independently associated with increased risk for symptomatic ICH (sICH rate - 9·8 per 1000 patient-years with CMBs compared to 2.6 without CMBs)[22]. In the NAVIGATE-ESUS trial, use of rivaroxaban in patients with cryptogenic stroke was associated with a 4-fold increase in the risk of ICH, and the risk was greater with a higher CMB burden[23]. Some studies have reported higher rates of ICH, disability and mortality in patients with >10 CMBs when treated with intravenous thrombolysis for ischaemic stroke, especially in older age and with longer treatment delays[24]. However, others have not found similar increased bleeding risks with thrombolysis[25].

CMBs – To treat or not to treat?

Patients with recent ischaemic stroke or TIA are at risk of recurrent ischaemic events, but the risk of ICH with antithrombotic therapy is greater in the presence of CMBs. This has led to a therapeutic conundrum in patients with a history of stroke and CMBs detected on MRI, with concerns expressed regarding the use of antithrombotic treatment, especially anticoagulants[2,16,23]. It has been suggested that patients with lobar ICHs and numerous lobar CMBs, with the possibility of underlying CAA and associated high risk of rebleeding, should not receive anticoagulants[2].

However, there is increasing evidence that CMBs are not only markers of a haemorrhage-prone arteriopathy but also markers of recurrent ischaemic events[12]. Recent data has shown that the absolute risk of recurrent ischaemic stroke is higher than the risk of ICH in patients with ischaemic stroke or TIA and CMBs, even with a high CMB burden[10,22,23,26]. In a pooled analysis of data from 38 cohort studies in the Microbleeds International Collaborative Network, the rate of recurrent ischaemic stroke was 64/1000 person-years, compared to symptomatic ICH rate of 27/1000 person-years, in the presence of ≥10 CMBs[10]. In the CROMIS-2 study of patients on anticoagulation therapy for AF following ischaemic stroke or TIA, the absolute event rate of ischaemic stroke in patients with CMBs (24.1 per 1000 patient-years) was much higher than the absolute event rate of symptomatic ICH (9.8 per 1000 patient-years)[22]. A recent study of patients with acute ischaemic stroke and AF treated with oral anticoagulants has yielded similar results. The presence and burden of CMBs were associated with an increase in vascular events (ICH, ischaemic stroke or vascular death) on long term follow up, and the absolute rates of ischaemic stroke were higher than those of ICH at all levels of CMB burden[26]. In a subgroup analysis of the NAVIGATE-ESUS trial, the presence of CMBs did not influence the risk of ICH in patients with cryptogenic stroke treated with rivaroxaban[23]. Further, no interaction was noted between single or dual antiplatelet therapy and the presence of CMBs for the outcomes of recurrent ischaemic or haemorrhagic stroke in patients with lacunar infarcts in the SPS3 trial[7]. More recent data demonstrate that starting antiplatelet treatment may not be associated with an increased risk of bleeding in the presence of CMBs even in patients with ICH. In the RESTART trial, CMB presence, burden or location was not associated with a higher risk of recurrent ICH in patients treated with antiplatelet therapy following an ICH[27].

These data suggest that the CMB presence, pattern or burden should not influence the decision to select appropriate antithrombotic therapy for secondary stroke prevention. Withholding antithrombotic treatment based on the presence of CMBs is not supported by current evidence[10,12,23,26,28].

CMBs – more uncertainties

Management of patients with CMBs poses several more therapeutic dilemmas. Several factors such as blood pressure variability and control and concurrent anti-thrombotic drug use can increase ICH risk, in addition to the presence of CMBs. There is no data regarding their relative contribution to ICH risk[7]. The ongoing APACHE-AF trial is expected to provide more insights into the use of NOACs in patients with AF and a recent ICH[29].

There is a well-known geographical variation in ICH risk, with ICH being commoner in Asian, especially Far Eastern, populations. Their vascular risk factor profile is different, with a higher prevalence of hypertensive arteriopathy. Asians also have a higher CMB prevalence compared to Western populations, in both ischaemic stroke and ICH patient groups[12,16,23]. Their CMB distribution is different, with higher rates of non-lobar (deep or infratentorial) CMBs, and hypertensive arteriopathy rather than CAA is believed to contribute to the elevated ICH risk in Asians[30]. The balance of risk for developing ICH compared to ischaemic stroke in the presence of CMBs appears to be different between Asian and Western populations, with Asians with CMBs more likely to develop ICH and Western populations more likely to develop ischaemic stroke[11]. Further studies are needed to better understand the complex effects of ethnicity and genetics on CMB prevalence and associated ICH risk.

Of particular interest are the intriguing results of a recent study which identified *Streptococcus mutans*, an oral pathogen responsible for dental caries, in a large number of stroke patients with CMBs, suggesting a possible association between the oral microbiome and cerebral microbleeds[31]. It has been postulated that *S. mutans* expressing the cnm gene can enter the blood stream from the oral cavity, attach to the cerebral vasculature, disrupt the blood-brain barrier, and lead to the development of CMBs[31]. This raises the exciting possibility of treating CMBs with antibiotics to reduce stroke risk.

Key learning points

- Cerebral microbleeds (CMBs) are a radiological biomarker of cerebral microangiopathy.
- Lobar CMBs are associated with cerebral amyloid angiopathy in superficial perforating arteries, and subcortical CMBs with hypertensive arteriopathy in deep perforating arteries.
- CMBs are more prevalent in patients with both haemorrhagic stroke and ischaemic stroke, and are a marker for small vessel disease.
- In patients with intracerebral haemorrhage (ICH), CMBs increase risk of recurrent ICH, and in patients with ischaemic stroke, CMBs increase risk of recurrent stroke, both ischaemic and haemorrhagic.
- The absolute event rate is higher for ischaemic stroke than for ICH in patients with stroke and CMBs.
- There is no evidence to support a policy of with-holding antithrombotic treatment in patients with stroke and CMBs.

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