Cerebral microbleeds in acute ischemic stroke
A red flag for IV thrombolysis

IV thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) is currently an approved therapy for acute ischemic stroke within 4.5 hours after onset. However, IVT increases the risk of symptomatic intracerebral hemorrhage (sICH), which is associated with poor functional outcome and mortality.1 The identified risk factors for IVT-related sICH include advanced age, hyperglycemia, elevated blood pressure, stroke severity, infarct volume, pretreatment antithrombotic use, and imaging surrogates of cerebral small vessel disease.2,3

Cerebral microbleeds (CMBs) correspond to focal hemosiderin deposits and represent a form of cerebral small vessel disease. Hypertension vasculopathy (arteriolosclerosis) and cerebral amyloid angiopathy represent the 2 main types of small vessel diseases. Hypertensive vasculopathy and cerebral amyloid angiopathy cause about 55% of all spontaneous intracerebral hemorrhage.3 CMBs, as surrogates of small vessel disease, are strongly associated with spontaneous ICH,4 but they are not visible on CT.

The currently recommended imaging modality to evaluate acute ischemic stroke patients for IVT is head CT, but should we instead recommend MRI? Can we identify patients with increased risk of post-IVT sICH by detection of CMBs with gradient-recalled echo or susceptibility-weighted imaging?6 Sixty percent of patients with spontaneous ICH have CMBs and, interestingly, 30% of patients presenting with ischemic stroke have CMBs.5 Whether preexisting CMBs among eligible patients for IVT increase the risk of ICH and whether one should withhold thrombolytic therapy in these patients remains controversial.6,7

In this issue of Neurology®, Charidimou and Shoamanshe8 performed an updated meta-analysis of the risk of both ICH and poor functional outcome in acute ischemic stroke patients treated with IVT and evidence of pretreatment CMBs on MRI. The authors identified 8 relevant studies assessing sICH risk, including 2,601 (624 with CMBs and 1,977 without CMBs) acute ischemic stroke patients treated with IV rtPA. Compared to those without CMBs, those with CMBs had a higher incidence of sICH (5% vs 3%) with an odds ratio (OR) of 2.18 (95% confidence interval [CI] 1.12–4.22; p = 0.021). In addition, the authors assessed the risk of poor functional outcome (i.e., mRS ≥2) at 3–6 months, according to the presence of pretreatment CMBs. Drawing from 4 studies, they found that the 445 individuals with CMBs had a higher incidence of poor outcome than the 1,220 without CMBs (52% vs 41%) with an OR of 1.58 (95% CI 1.18–2.14; p = 0.002).

These results in acute ischemic stroke patients treated with IVT show that the presence of pretreatment CMBs is associated with an increased risk of both sICH and poor functional outcome, and thus suggest a crucial factor in clinical decision-making. Nevertheless, do these findings justify withholding IVT in patients with CMBs? The answer remains uncertain. First, in this meta-analysis, the authors could not adjust for other risk factors for sICH and predictors of poor functional outcome (age, onset to treatment, infarct volume, reperfusion, pretreatment modified Rankin Scale score). Second, this study did not address whether acute ischemic stroke patients with CMBs treated with IVT have a worse functional outcome than those not treated with IVT. Further studies are needed to answer to this major question.

In addition, the severity of the underlying small vessel disease might also modify the threshold for post-IVT sICH. Given that the risk of sICH is associated with the number of CMBs, the CMB burden, rather than presence, may have greater effect on post-IVT sICH risk. A recent meta-analysis on this topic found that high CMB burden (more than 10 CMB) was strongly and independently associated with post-IVT sICH.9

In current clinical practice, these results have limited generalizability. Noncontrast head CT remains the recommended imaging modality to evaluate eligible patients for IVT because in most settings it is much faster to perform. The benefits of time saving in IVT treatment are well-established10; so far, the benefit of ruling out CMBs has not.

Increased evidence indicates that presence and burden of CMB may herald an increased risk of sICH...
among acute ischemic stroke patients treated with IVT. This hypothesis-generating meta-analysis provides important additional perspective with the identification of an increased risk of poor functional in acute ischemic stroke patients treated with IVT and presence of CMBs. Although further studies will need to adjust for confounders to assess the relationship among CMBs, sICH, and poor functional outcome accurately, this meta-analysis highlights potential advances in the selection of acute ischemic stroke patients for IVT. A specific evaluation of the net clinical benefit of IVT among patients with CMBs remains to be performed before implementing a systematic detection of CMBs for acute stroke patients and offering them an adapted reperfusion strategy.

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DISCLOSURE
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REFERENCES