Cerebral Microbleeds and Thrombolysis-Associated Intracerebral Hemorrhage
Cause for Concern, or Just a Distraction?

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See related article, p 2458.

Thrombolysis with intravenous recombinant tissue-type plasminogen activator (r-tPA)—still the only licensed therapy in hyperacute treatment ischemic stroke—has a clear population benefit on functional outcome, but there are likely to be individuals for whom the risk of severe harm outweighs benefit. The most dreaded complication is early symptomatic intracranial hemorrhage (sICH), which occurs in 6.8% of r-tPA–treated patients within 7 days when compared with 1.3% in controls, and is associated with higher disability.1

Unfortunately, it is not yet possible to predict any subgroup of patients more likely to be harmed than helped by intravenous thrombolysis, despite efforts to develop pre-dictive sICH scores incorporating clinical and simple computed tomography–based imaging variables: such scores have c-statistics in the range of 0.62 to 0.70, making them unhelpful for individual treatment decisions.2 Limited predictive power reflects limited understanding of the underlying mechanisms of r-tPA–associated sICH, which are diverse,3 ranging from hemorrhagic transformation of the acute infarct (associated with ischemic injury, blood–brain barrier compromise, and recanalization-related reperfusion injury) to remote or multifocal bleeding (more likely related to a widespread bleeding-prone small vessel vasculopathy, and found in 28% of r-tPA–associated ICH cases in an observational study).4

Cerebral microbleeds (CMBs) are common in healthy older populations and hospital cohorts with stroke or cognitive impairment. CMBs could be linked with thrombolysis-associated sICH as a radiological marker for the small vessel diseases that underlie most spontaneous ICH, including hypertensive arteriopathy and cerebral amyloid angiopathy (CAA). CMBs develop rapidly in acute ischemic stroke (in 12% of patients in the first 24 hours in 1 study),5 and under the effect of r-tPA such usually self-limiting CMBs could evolve into a sICH. A strictly lobar pattern of CMBs may be of particular interest for sICH risk, as it is (in hospital cohorts) highly specific for CAA pathology,6,7 a potent cause of ICH. Indeed, CAA-related and thrombolysis-associated intracerebral hemorrhages have similarities, including a tendency to occur in multiple lobar regions, and an association with increasing age and dementia. Small neuropathological studies link CAA to r-tPA–associated ICH,8,9 as does a positron emission tomography study showing higher neocortical amyloid retention among patients with r-tPA–associated ICH when compared with those without.10 Thus, whether the presence, or pattern, of CMBs on pretreatment magnetic resonance imaging (MRI) predicts the risk of r-tPA–related sICH is a timely and topical research question.

In the current issue of Stroke, Turc et al11 contribute important new data to the debate. In 2 French centers (where MRI is the first-line prethrombolysis imaging), they prospectively investigated whether CMBs on prethrombolysis gradient echo T2* MRI are associated with sICH risk or 3-month functional outcome (modified Rankin Scale). Neuroradiologists, blinded to clinical data, rated CMBs using the validated Microbleed Anatomic Rating Scale. Among 717 included patients, 150 (20.9%) had ≥1 CMBs, and 25 (3.5%) had ≥5. CMB burden was associated with worse 3-month modified Rankin Scale in univariate shift analysis (odds ratio, 1.07; 95% confidence interval, 1.00–1.15 per 1-CMB increase; P=0.049), but not after adjustment for confounding factors including age and hypertension (odds ratio, 1.03; 95% confidence interval, 0.96–1.11 per 1-CMB increase; P=0.37). The results remained nonsignificant when taking into account CMBs location or presumed underlying vasculopathy. CMB presence, burden, location, and presumed underlying vasculopathy were not significantly associated with sICH (which occurred in 3.8%–9.1% depending on the definition used).

This study clearly contributes significant new data, but it is important to consider potential limitations and place it in the context of other relevant studies. The cohort was a subset of a much larger number of r-tPA–treated patients (n=931); ≈23% of the patients treated did not undergo the required MRI sequences and were excluded. Those excluded had more severe strokes (higher National Institutes of Health Stroke Scale Score), which could itself be associated with worse outcome and sICH. However, National Institutes of Health Stroke Scale Score was not associated with CMB presence or burden, providing some reassurance that this potential bias did not importantly affect the results. The authors found no relationship between probable CAA (ie, strictly lobar CMBs) and sICH, but the total number of such patients was only 45 (6.3%), providing limited power. Moreover, the results seem discrepant with most previous published studies of CMBs and r-tPA–associated ICH risk. A recent updated pooled

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meta-analysis in a total of 2028 patients from 10 eligible studies found that of the 23% of patients with pretreatment CMBs, 8.5% experienced sICH when compared with 3.9% of those without CMBs; for those treated with intravenous r-tPA, the pooled odds ratio was 2.87 (95% confidence interval, 1.76–4.69), which could not be accounted for by confounding factors associated with CMBs (eg, age, hypertension; Charidimou et al13). The direction of association between CMBs and sICH risk was remarkably consistent. Indeed, Sallem et al also report an increase in the odds of sICH with increasing CMB burden (eg, odds ratio for NINDS defined sICH per additional CMB was 1.07 (95% confidence interval 0.97–1.17), albeit not statistically significant.

Given the variation in findings from studies to date, we cannot yet conclude whether CMBs on pretreatment MRI should influence decision-making in thrombolytic treatment for acute ischemic stroke. Since r-tPA related ICH is rare, a definitive answer will need large-scale pooled individual patient data meta-analyses of high quality prospective studies. These will ideally include standardized and reliable classification of CMBs according to their location and burden, and full adjustment for potential confounding factors. With larger samples, it should be possible to test the hypotheses that: (1) strictly lobar CMBs (presumably reflecting CAA) are a predictor of r-tPA related ICH; and (2) that there is a dose-response relationship between CMBs and bleeding risk, as shown in some previous studies. It will be important to test whether CMBs presence, distribution or burden are linked to particular sICH patterns, assessed using standardized classification systems. Specifically, ICH remote from the infarct may be more likely to be associated with CMBs. Most crucially, future studies will need to determine whether pretreatment CMBs are independently and significantly associated with worse long term functional outcomes for patients, the ultimate test of clinical relevance.

The current study included only intravenous r-tPA-treated patients, but recent positive trials of acute endovascular therapy in ischemic stroke have ushered in a new era of acute stroke treatment. There are very limited data on whether CMBs are related to the risk of sICH following such endovascular treatment. A recent study reported CMBs in 37 of 206 (18%) patients treated with mechanical thrombectomy, and found no differences in parenchymal hemorrhage, mortality or 90 day outcome in the group associated with CMBs.15

So what should clinicians do now when faced with the finding of CMBs in acute ischemic stroke patients being considered for intravenous thrombolysis? Although the balance of published evidence suggests that CMBs are independently linked to increased sICH risk, the data are far from conclusive, as shown in the new study of Turec et al. The published studies have potential methodological weaknesses, including selection bias, and measured or unmeasured confounding factors. Thus, until more definitive data are available, CMBs on MRI should not be considered a contraindication to intravenous r-tPA in otherwise eligible patients. However, in the heat of acute stroke therapy decisions, numerous CMBs (especially in a strictly lobar distribution) could still cause anxiety. Although large pooled analyses failed to identify specific subgroups likely to suffer harm from r-tPA, CMBs might reasonably be taken into account as just 1 factor that could potentially affect outcome (along with prestroke dementia, leukoaraiosis, poorly controlled hypertension, etc) to help guide risk–benefit assessment in difficult decisions. If future analyses do show a clear and strong link between CMBs and sICH or long-term outcome after thrombolysis, this could help clinicians design future acute ischemic stroke trials, make safer decisions, improve patient outcomes, and would provide additional support for the routine availability of MRI in hyperacute stroke treatment and research.

Disclosures
None.

References
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