

CT scanning to diagnose CAA: back to the future?



Most intracerebral haemorrhages are due to cerebral small vessel diseases hypertensive arteriopathy (arteriolosclerosis), which affects deep perforating vessels, and cerebral amyloid angiopathy (CAA), which affects superficial cortical and leptomeningeal vessels. Diagnosis of CAA is important because it has a high recurrence risk (7.4% per year in a pooled analysis of cohort studies)¹ and might require specific prevention strategies (eg, modifying the use of antithrombotic drugs) or, in the future, disease-modifying treatments targeting vascular β -amyloid.² MRI with blood-sensitive sequences can detect haemorrhagic small vessel disease biomarkers, including cerebral microbleeds and cortical superficial siderosis,³ making it the best in-vivo diagnostic modality for CAA. By contrast, although widely available as the first diagnostic test for acute intracerebral haemorrhage, the value of CT for diagnosing CAA is uncertain.

In *The Lancet Neurology*, Mark A Rodrigues and colleagues did a diagnostic accuracy study⁴ of acute non-contrast CT brain scans in a prospective population-based inception cohort study of adults with first-ever intracerebral haemorrhage who died and underwent research autopsy. Of the 62 participants with lobar intracerebral haemorrhage, 36 (58%) were associated with moderate or severe CAA compared with 26 (42%) that were associated with absent or mild CAA, and were independently associated with subarachnoid blood extension (32 [89%] of 36; $p=0.014$), finger-like projections associated with the haematoma (14 [39%] of 36; $p=0.043$), and APOE $\epsilon 4$ possession (18 [50%] of 36; $p=0.0020$). The diagnostic criteria for CAA-associated lobar intracerebral haemorrhage had excellent discrimination (c statistic 0.92, 95% CI 0.86–0.98), confirmed by internal validation. For the rule-out criteria, neither subarachnoid haemorrhage nor APOE $\epsilon 4$ possession had 100% sensitivity (95% CI 88–100), whereas for the rule-in criteria, subarachnoid haemorrhage and either APOE $\epsilon 4$ possession or finger-like projections had 96% specificity (95% CI 78–100). A simplified CT-only model found subarachnoid haemorrhage alone had 89% sensitivity (95% CI 73–96), whereas subarachnoid haemorrhage and finger-like projections had 100% specificity (95% CI 84–100).

The study was of high methodological quality, including population-based recruitment, blinded

assessment of the index diagnostic test, and clear presentation of diagnostic accuracy and statistical uncertainty. Autopsy with standardised neuropathological evaluation is the best available reference standard to decide whether CAA is likely to have caused a particular intracerebral haemorrhage, although, as the authors note, other non-CAA small vessel disease (eg, arteriolosclerosis or lipohyalinosis) frequently co-existed with CAA and so might have also contributed to some lobar intracerebral haemorrhage.

The Edinburgh criteria could open a new chapter in CAA diagnosis because CT scanning is well tolerated by almost all acute patients with intracerebral haemorrhage and is more widely available than MRI, especially in countries with poor brain imaging resources. If CAA could be accurately diagnosed on the basis of acute CT findings, this diagnosis would rapidly provide clinicians, patients, and families with important information on prognosis in the acute stage of intracerebral haemorrhage that otherwise might be available only later or not at all.

However, substantial limitations need to be addressed before the Edinburgh criteria might be useful for routine clinical practice. Most importantly, external validation must ensure that the excellent model performance does not relate to specific circumstances of patient population, recruitment, CT scan rating, or analysis. The included population was biased towards older patients with more severe intracerebral haemorrhage, early death, and other adverse prognostic features, so might not be applicable to patients with mild intracerebral haemorrhage in whom long-term management plans are needed. Furthermore, progressive cognitive impairment and transient focal neurological episodes are increasingly recognised as presenting syndromes of CAA,⁵ which were not included in this study.

An important next step is to compare the Edinburgh CT-based criteria to the established and widely used MRI-based Boston diagnostic criteria, which, using strictly lobar bleeding and cortical superficial siderosis, have excellent sensitivity and good specificity for CAA,⁶ ideally using a brain tissue diagnosis as a common reference standard. Unfortunately, the authors could only obtain MRI in seven patients, so could not investigate this. Future studies should also determine whether CT-defined

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intracerebral haemorrhage associated with CAA is associated with a high risk of intracerebral haemorrhage recurrence (as is the case for MRI-diagnosed intracerebral haemorrhage associated with CAA),¹ which would add validity and clinical prognostic value.

The new CT-based criteria rely on detecting finger-like projections, which were very tightly linked with CAA-associated intracerebral haemorrhage, and were absent in all non-CAA lobar intracerebral haemorrhage; a key challenge is to better define these projections (currently subjective and guided by representative images on a rating form), especially for non-neuroradiologists, to improve the modest inter-rater agreement of 0.60 (0.36–0.83). Reliability testing in other populations and observers will be important, while future research with machine learning techniques could help to objectively and reproducibly diagnose intracerebral haemorrhage associated with CAA on CT images without inter-rater variation. This study was an acute study with a median time of 5 h (IQR 3–18) from intracerebral haemorrhage to CT scan. The prevalence of finger-like projections and subarachnoid haemorrhage are likely to reduce over time, by contrast with stable MRI findings in the Boston criteria that can be applied at any time. Further work to establish the dynamic evolution, changing diagnostic accuracy with time, and underlying mechanisms of these CT markers will be important.

Finally, the full criteria also require APOE genotyping, which is not routinely available, even in specialist

centres. This requirement will limit immediate application in clinical practice, but if the criteria are externally validated and are shown to add important clinical value, it would make a strong argument for allocating resources to make APOE testing more widely available. In the meantime, the Edinburgh CT and genetic criteria offer researchers and clinicians the exciting prospect of rapid and accurate diagnosis in this most deadly form of intracerebral haemorrhage.

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