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Intracerebral hemorrhage and small vessel disease

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Spontaneous intracerebral hemorrhage (ICH) is a serious life-threatening event with the highest morbidity and mortality. ICH is a global burden affecting approximately 2 million people annually. It is estimated that more than one-third of ICH patients die within the first month of onset, and 40% of survivors remain disabled. However, there is an absence of evidence-proved therapies for ICH.[1]

Cerebral small vessel disease (CSVD) is a pathological disorder, which affects perforating arterioles, capillaries, and probable venules in the brain parenchyma or the subarachnoid space. The sporadic small vessel disease (SVD) is classified into hypertensive arteriopathy (HA) caused by long-term hypertension and vascular risk factors, and cerebral amyloid angiopathy (CAA) characteristic by the amyloid-β (Aβ) deposition in cortical and leptomeningeal small-to-medium-sized arteries, arterioles, and capillaries. While CSVD in the chronic phase can be clinically silent,[2] a wide range of clinical manifestations is related to CSVD, such as stroke, mood disorders, and cognitive impairment. The coexistence and location of CSVD may give a clue to the etiology of ICH.

Imaging Markers of Cerebral Small Vessel Disease

Magnetic resonance imaging (MRI) is increasingly performed in patients with ICH, and MRI-based CSVD markers have been defined. In 2013, the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria was published for reporting brain MRI markers of SVD.[3] Lesions on conventional MRI include enlarged perivascular space (EPVS), white matter hyperintensities (WMH), and lacunes of presumed vascular origin. T2*-gradient recall echo (GRE) and susceptibility-weighted imaging (SWI) are novel techniques to detect imaging markers including cerebral microbleeds (CMBs), cortical superficial siderosis (cSS), and acute convexity subarachnoid hemorrhage (cSAH), which are invisible on conventional T1- and T2-weighted sequences.

Cerebral Microbleed and Intracerebral Hemorrhage

CMBs are small (2–5 mm in diameter), round to ovoid hypointense lesions on T2*-GRE and SWI. Lobar microbleeds are commonly seen in patients with CAA and deep CMBs may occur as a result of hypertension. Similar to the supratentorial region, superficial cerebellar CMBs in gray matter and vermis are independently associated with CAA-ICH, while cerebellar white matter CMBs are more likely hypertensive, and patients may have coexisted supratentorial deep CMBs. Mixed-location hemorrhage is frequent in the clinical setting, whereas the underlying type of SVD may differ. Lobar/total CMB ratio and presence of cSS may help further differentiate the underlying SVD in ICH patients.[4] The lobar/total CMB ratio was significantly correlated with lobar ICH and cSS, implicating that it may be a novel biomarker of underlying CAA. This is of great interest because it may help include more CAA patients in the future clinical trials.

CMBs are associated with an increased risk of stroke. A meta-analysis pooling 15,693 participants from multiple stroke cohorts and stroke-free populations demonstrated that CMBs increased the risk of ICH by 3.82-fold compared with a mere 2-fold increased risk of incident ischemic stroke.[5]

CMBs have played a role in clinical trials to evaluate future bleeding risk in populations with antithrombotic therapy. In the Clinical Relevance of Microbleeds in Stroke-2 (CROMIS-2) and the Hemorrhage Predicted by Resonance in Patients Receiving Oral Anticoagulants (HERO), CMB

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is an independent predictor of ICH for patients prescribed oral anticoagulants.[6,7] Alternative treatment may be considered in such a group. A subgroup analysis of the REstart or STop Antithrombotics Randomised Trial (RESTART) suggested that restarting antiplatelet therapy in ICH patients with CMB might be safe.[8]

Cortical Superficial Siderosis and Intracerebral Hemorrhage

cSS defined as a characteristic gyriform hypointense signal pattern on T2*-GRE or SWI without corresponding lesions on conventional sequence such as fluid-attenuated inversion recovery (FLAIR) reflects hemosiderin deposited on the outermost surface of the cortex or the subarachnoid space. As a novel key hemorrhagic feature of CAA, cSS has been added into the modified Boston Criteria for *in vivo* diagnosis of CAA as neuroimaging evidence to increase the sensitivity.

cSS strongly predicts first and recurrent lobar ICH. Moreover, the risk of recurrence is parallel with the burden of cSS. A recent meta-analysis of six studies showed that annual ICH incidence was higher in patients with cSS than those without (11.1% *vs*. 3.9%), and was increasingly higher with the extent of cSS (9.1% for focal cSS *vs*. 12.5% for disseminated).[9] cSS multifocality was associated with a higher annual ICH recurrence rate and was the only independent predictor of future ICH recurrence (hazard ratio [HR] 3.19; 95% confidence interval [CI] 1.77–5.75) from other MRI SVD markers.[10] Severe cSS progression over time was independently associated with increased future ICH risk (HR 5.90; 95% CI 1.30–26.68).[11]

Convexity Subarachnoid Semorrhage and Intracerebral Hemorrhage

Acute cSAH is defined as linear hyperintense signal on FLAIR sequence with or without corresponding hypointense signal on T2*-GRE or SWI in the subarachnoid space affecting at least one cortical sulci of the cerebral convexities. cSAH is a key marker of the acute focal bleeding event strongly associated with transient focal neurological episodes (TNFE) similar to transient ischemic attack (TIA). Unlike cSS, acute cSAH can also be observed on computed tomography (CT). According to the recently devised "Edinburgh CT and genetic diagnostic criteria" for CAA, the coexistence of cSAH on CT, finger-like projection, and apolipoprotein E (*APOE*) ε4 implicates a high risk of moderate-to-severe CAA with a specificity of 96%.[12] It enables rapid etiological assessment for those who are unable to undergo MRI.

In a recent study of CAA-ICH survivors, the risk of recurrent ICH was seven-fold higher in cSAH present group when compared with those without.[13] Another CT-based study validated that cSAH irrespective of spatial relationship from ICH was associated with cSS and higher recurrence risk.[14] It is also implicated that *APOE* ε2 allele instead of ε4 allele contributes to cSAH/cSS because *APOE* ε2 allele may promote vasculopathic changes and vessel rupture, while *APOE* ε4 favors perivascular amyloid deposition and cortical microbleeds.[15]

The exact underlying pathophysiology of cSAH and cSS is unclear. Cumulative evidence suggests that cSAH is the acute form of cSS. The prevailing view is that rupture of brittle leptomeningeal or superficial cortical vessels severely affected by Aβ deposition might lead to focal bleeding into the subarachnoid space.[16] Corresponding with clinical findings, pathology-confirmed cSS was frequently observed with advanced CAA features such as concurrent concentric splitting of the leptomeningeal vessels but reduced CAA severity in cortical vessels. Furthermore, no association between cSS and CMBs was found, which may implicate different pathophysiological entities.[16]

White Matter Hyperintensities and Intracerebral Hemorrhage

WMH characterized by hyperintensities on FLAIR sequence are very common in aging populations. Recent evidence suggests that posterior, peripheral punctuate WMH reflect CAA and deep, peri-basal ganglia (BG) WMH is evidence of HA. Extensive WMH doubled the risk of ischemic stroke and tripled the risk of ICH.[5] Nonetheless, whether WMH severity correlates with larger hematoma volume and hematoma expansion is still controversial and requires further investigation in larger studies.

Lacune and Intracerebral Hemorrhage

Lacunes as covert brain infarct without acute neurological deficit and disability are round or ovoid, subcortical, fluid-filled cavities with a diameter of 3 to 15 mm, located in the lobar white matter, BG, thalamus, and infratentorial regions. In line with other MRI markers, the topographical distribution of lacunes may give a clue to the subtypes of SVD. In an ICH cohort, lobar lacunes were more commonly seen in CAA (20.4% *vs*. 5.7%), while deep lacunes were more frequent in hypertensive ICH (15.2% *vs*. 2.1%).[17] This was confirmed by an Asian study. Tsai *et al*[18] found lobar lacune number was independently associated with cerebral amyloid burden using Pittsburgh Compound B positron emission tomography. A large-scale meta-analysis concluded that lacunes doubled the risk of incident stroke, of which the risk of ICH was even higher, and were also associated with increased mortality (HR 1.64; 95% CI 1.40–1.91; $P < 0.001$).[5]

Enlarged Perivascular Space and Intracerebral Hemorrhage

EPVS is commonly detected in elderly populations on T2-weighted sequences. EPVS in centrum semiovale (CSO-EPVS) is a marker of CAA, while a predominance of EPVS in BG (BG-EPVS) is generally caused by HA.

The severe burden of CSO-EPVS may be an early predictor of future hemorrhagic events. A study of CAA-ICH patients found that among multiple MRI markers high-degree CSO-EPVS along with cSS, rather than overall burden were independent predictors of ICH recurrence.[19] The global burden of EPVS was consistently associated with a greater risk of incident ICH in a population-based study of 1678 participants.[20] EPVS is speculated as evidence of impaired cerebral glymphatic drainage and

elevated arterial Aβ burden, promoting the formation of cSS and symptomatic ICH eventually.

Future Directions

Advanced MRI technology to investigate SVD markers has shed light on the impact of the lesions on future cerebral hemorrhagic events. These MRI markers may be useful to stratify the bleeding risk of CAA patients, a subgroup of whom present with ICH while others come to medical attention due to cognitive decline. However, there is still little therapeutic intervention to be offered in clinical practice. This fact should give motivation for those in the field to continue mechanistic and investigative studies to devise novel interventions for treatment.

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Conflicts of interest

None.

References

1. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. Lancet 2018;392:1257–1268. doi: 10.1016/S0140-6736(18)31878-6.
2. Das AS, Regenhardt RW, Vernooij MW, Blacker D, Charidimou A, Viswanathan A. Asymptomatic cerebral small vessel disease: Insights from population-based studies. J Stroke 2019;21:121–138. doi: 10.5853/jos.2018.03608.
3. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al*. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–838. doi: 10.1016/S1474-4422(13)70124-8.
4. Blanc C, Viguier A, Calviere L, Planton M, Albucher JF, Rousseau V, *et al*. Underlying small vessel disease associated with mixed cerebral microbleeds. Front Neurol 2019;10:1–8. doi: 10.3389/fneur.2019.01126.
5. Debette S, Schilling S, Duperron MG, Larsson SC, Markus HS. Clinical significance of magnetic resonance imaging markers of vascular brain injury: A systematic review and meta-analysis. JAMA Neurol 2019;76:81–94. doi: 10.1001/jamaneurol.2018.3122.
6. Martí-Fàbregas J, Medrano-Martorell S, Merino E, Prats-Sánchez L, Marín R, Delgado-Mederos R, *et al*. MRI predicts intracranial hemorrhage in patients who receive long-term oral anticoagulation. Neurology 2019;92:e2432–e2443. doi: 10.1212/WNL.0000000000007532.
7. Wilson D, Ambler G, Shakeshaft C, Brown MM, Charidimou A, Al-Shahi Salman R, *et al*. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): A multicentre observational cohort study. Lancet Neurol 2018;17:539–547. doi: 10.1016/S1474-4422(18)30145-5.
8. Al-Shahi Salman R, Minks DP, Mitra D, Rodrigues MA, Bhatnagar P, du Plessis JC, *et al*. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: Subgroup analyses of the RESTART randomised, open-label trial. Lancet Neurol 2019;18:643–652. doi: 10.1016/S1474-4422(19)30184-X.
9. Charidimou A, Boulouis G, Greenberg SM, Viswanathan A. Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy: a meta-analysis. Neurology 2019;93:e2192–e2202. doi: 10.1212/WNL.0000000000008590.
10. Charidimou A, Boulouis G, Roongpiboonsopit D, Auriel E, Pasi M, Haley K, *et al*. Cortical superficial siderosis multifocality in cerebral amyloid angiopathy: a prospective study. Neurology 2017;89:2128–2135. doi: 10.1212/WNL.0000000000004665.
11. Pongpitakmetha T, Fotiadis P, Pasi M, Boulouis G, Xiong L, Warren AD, *et al*. Cortical superficial siderosis progression in cerebral amyloid angiopathy: prospective MRI study. Neurology 2020;94:e1853–e1865. doi: 10.1212/WNL.0000000000009321.
12. Rodrigues MA, Samarasekera N, Lerpiniere C, Humphreys C, McCarron MO, White PM, *et al*. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. Lancet Neurol 2018;17:232–240. doi: 10.1016/S1474-4422(18)30006-1.
13. Raposo N, Charidimou A, Roongpiboonsopit D, Onyekaba M, Gurol ME, Rosand J, *et al*. Convexity subarachnoid hemorrhage in lobar intracerebral hemorrhage: a prognostic marker. Neurology 2020;94:e968–e977. doi: 10.1212/WNL.0000000000009036.
14. Li Q, Zanon Zotin MC, Warren AD, Ma Y, Gurol E, Goldstein JN, *et al*. CT-visible convexity subarachnoid hemorrhage is associated with cortical superficial siderosis and predicts recurrent ICH. Neurology 2020;96:e986–e994. doi: 10.1212/wnl.0000000000011052.
15. Charidimou A, Zonneveld HI, Shams S, Kantarci K, Shoamanesh A, Hilal S, *et al*. APOE and cortical superficial siderosis in CAA: meta-analysis and potential mechanisms. Neurology 2019;93:e358–e371. doi: 10.1212/WNL.0000000000007818.
16. Charidimou A, Perosa V, Frosch MP, Scherlek AA, Greenberg SM, van Veluw SJ. Neuropathological correlates of cortical superficial siderosis in cerebral amyloid angiopathy. Brain 2020;143:3343–3351. doi: 10.1093/brain/awaa266.
17. Pasi M, Boulouis G, Fotiadis P, Auriel E, Charidimou A, Haley K, *et al*. Distribution of lacunes in cerebral amyloid angiopathy and hypertensive small vessel disease. Neurology 2017;88:2162–2168. doi: 10.1212/WNL.0000000000004007.
18. Tsai HH, Pasi M, Tsai LK, Chen YF, Lee BC, Tang SC, *et al*. Distribution of lacunar infarcts in Asians with intracerebral hemorrhage: a magnetic resonance imaging and amyloid positron emission tomography study. Stroke 2018;49:1515–1517. doi: 10.1161/STROKEAHA.118.021539.
19. Boulouis G, Charidimou A, Pasi M, Roongpiboonsopit D, Xiong L, Auriel E, *et al*. Hemorrhage recurrence risk factors in cerebral amyloid angiopathy: comparative analysis of the overall small vessel disease severity score versus individual neuroimaging markers. J Neurol Sci 2017;380:64–67. doi: 10.1016/j.jns.2017.07.015.
20. Duperron MG, Tzourio C, Schilling S, Zhu YC, Soumaré A, Mazoyer B, *et al*. High dilated perivascular space burden: a new MRI marker for risk of intracerebral hemorrhage. Neurobiol Aging 2019;84:58–165. doi: 10.1016/j.neurobiolaging.2019.08.031.

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