What Causes Hematoma Enlargement in Lobar Intracerebral Hemorrhage? Novel Insights From a Genetic Study

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See related article, p 1490.

Intracerebral hemorrhage (ICH) accounts for 10% to 15% of all strokes worldwide.1 “Primary” ICH most often results from the rupture of a small penetrating artery, either associated with hypertensive arteriopathy or cerebral amyloid angiopathy (CAA). Whereas CAA-related ICH preferentially affects cortical–subcortical regions, hypertensive bleedings are located in “deep” areas of the brain such as the basal ganglia, thalamus, and brain stem. For both subtypes of ICH, hematoma size on initial brain scan and hematoma enlargement (HE) between the first and second brain imagings are strong and independent predictors of functional outcome.2,3 Hence, the prevention of HE by coagulation activation was recently evaluated as a treatment strategy in acute ICH in a large-scale randomized trial. Although recombinant coagulation factor VII reduced hematoma expansion, a positive effect on functional outcome after 3 months could not be demonstrated.4

One of the reasons for the lack of success of clinical trials so far might be our scarce knowledge regarding the pathophysiology that underlies hematoma growth. Observational studies reported HE to occur in approximately 30% to 40% of all ICH cases depending on the time spans to first and second brain imaging.5 Several predictors of HE have been identified so far, including clinical, laboratory, and radiological parameters.6,7 In this issue of Stroke, Brouwers et al8 identified the apolipoprotein E (APOE) genotype as a new risk factor for HE. APOE was initially characterized for its involvement in apolipoprotein E (APOE) function.10 In the general population, the APOE ε2 allele can be found in 50% to 90% of individuals, APOE ε4 in 5% to 35%, and APOE ε2 in 1% to 5%.10 In the present study, the authors retrospectively analyzed data from an ongoing prospective study that recruits patients with acute primary ICH. Cases were selected based on known APOE genotype and availability of a CT follow-up scan (n=510). The main finding of this study is that patients with lobar ICH were at higher risk of developing HE when carrying the APOE ε2 allele (OR, 2.65; 95% CI, 1.15–6.11). Importantly, the authors could demonstrate a certain “gene–dose” effect and furthermore found that the effect of APOE ε2 was pronounced in patients with the diagnosis of a probable/possible CAA according to the Boston criteria. In contrast, APOE ε4 had no effect on HE in lobar ICH, and both alleles had no effect on HE in deep ICH.

In the past, the APOE ε2 allele was found to be associated with ICH, but some controversies remained.11,12 The most profound evidence for such a link gives us a recent large-scale genetic association study of 2189 ICH cases and 4041 control subjects from 7 cohorts showing that APOE ε2 (OR, 1.82; 95% CI, 1.50–2.23 and APOE ε4 (OR, 2.20; 95% CI 1.85–2.63) are both independent risk factors for lobar ICH.13 In an additional study, the same group demonstrated that APOE ε2 increases the likelihood of a higher hematoma volume in lobar ICH, a worse functional outcome, and increased mortality. Interestingly, such an association could not be found for APOE ε4.14 The present study is in line with these studies and adds significantly to this field of research. It not only confirms the relevance of APOE ε2 in the pathophysiology of lobar ICH, but suggests that the higher hematoma volumes that were observed in patients with APOE ε2 are caused by a higher risk of HE.

With respect to the underlying pathophysiology, the authors explain their results along with the hypothesis that HE is caused by a mechanically induced rupture of small vessels in the direct vicinity of the initial bleeding site, also known as “cascade injury.”15,16 Because APOE ε2 and ε4 alleles promote perivascular Aβ deposition, but only ε2 is supposed to induce structural changes in amyloid-laden vessels, neighboring vessels exposed to APOE ε2 might be at higher risk to rupture.16 This may result in a higher likelihood of HE in APOE ε2 carriers. Although a plausible hypothesis, it is questionable whether the “cascade injury” is the major factor of HE at later time points (in this study, median time from symptom onset to first CT scan was 7.4 hours). Furthermore, it is not clear why the APOE ε4 and APOE ε2 allele are both associated with an increased risk of CAA-related lobar ICH if brain arterioles revealing the respective genotypes are that different in their risk of rupture. An explanation might be that the initial event leading to ICH is to some extent independent of Aβ deposits and the APOE genotype. Alternatively, APOE ε2 might have local inhibiting effects on blood coagulation, thereby leading to HE and larger ICH volumes. Another explanation would be that the type of the bleeding vessel...
itself is different between APOE genotypes. In a common neuropathological classification, CAA Type 1 is supposed to be associated with APOE ε4 and characterized by AB deposits in cortical capillaries. In contrast, CAA Type 2 is associated with APOE ε2 and shows AB deposits in leptomeningeal and cortical arteries, arterioles, and, rarely, veins. It is possible that bleeding from a cortical artery in CAA Type 2 is more likely to expand compared with a capillary leakage in CAA Type 1. As a limitation, this study is hampered by its retrospective design, which makes it difficult to reliably determine HE as the parameter of interest. One may notice that in the lobar ICH group, median time from symptom onset to first CT was as long as 7.4 hours with 25% of patients having their first scan not before 21.9 hours. Due to delayed CT scanning, several HE cases might have been overseen. As reported in the literature, HE most frequently develops (and can be observed) within the first 6 hours of symptom onset. Moreover, some studies reported that as much as 73% of patients assessed within 3 hours have some degree of hematoma enlargement thereafter. This explains why the rate of HE is remarkably low in this study (only 15% for lobar ICH, 10% for deep ICH). This raises the question whether a general assumption can be concluded from these data or whether the study reports an effect in a certain subgroup of patients with ICH only. Thus, the findings need to be replicated using an exploratory analysis. Stroke. 2007;38:1072–1075.


Disclosures

None.
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