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Cerebral Microbleeds and Macrobleeds: Should They Influence Our Recommendations for Antithrombotic Therapies?

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Abstract

Intracerebral hemorrhage (ICH, or macrobleeds) and cerebral microbleeds—smaller foci of hemosiderin deposits commonly detected by magnetic resonance imaging (MRI) of older adults with or without ICH—are both associated with an increased risk of future ICH. These hemorrhagic pathologies also share risk factors with ischemic thromboembolic conditions that may require antithrombotic therapy, requiring specialists in cardiology, internal medicine and neurology to weigh the benefits versus hemorrhagic risks of antithrombotics in individual patients. This paper will review recent advances in our understanding of hemorrhage prone cerebrovascular pathologies with a particular emphasis on use of these markers in decision making for antithrombotic use.

Keywords

intracerebral hemorrhage; cerebral; microbleed; macrobleed; anticoagulation; antithrombotic therapy; stroke prevention; leukoaraiosis; sulcal siderosis

INTRODUCTION

Intracranial hemorrhages are classified based on the primarily affected intracranial compartment and they include intraparenchymal (IPH), intraventricular (IVH), subarachnoid (SAH), subdural and epidural hemorrhages. Subdural and epidural hemorrhages are most commonly related to head trauma whereas SAH generally arise from ruptured cerebral aneurysms. This review will primarily focus on spontaneous intracerebral hemorrhage (ICH), a common type of stroke including IPH and IVH, that occurs in the absence of gross vascular pathology or trauma. ICH makes up 8-18% of all strokes based on published registries.[1,2] Bleeding within the brain parenchyma is classified as a macrobleed if it is greater than 5-10 mm in largest diameter as seen on head CT or MRI [Figure 1A].[3] IPH and IVH are usually symptomatic with the acute onset of headache, altered consciousness and focal neurologic deficits. Most recent population based estimates suggest an overall ICH

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Conflict of Interest

Kellen E. Haley, Steven M. Greenberg, and M. Edip Gurol declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

incidence of 24.6 per 100,000 person-years.[4] Intracerebral hemorrhage is a devastating condition, as it carries a one-month case fatality rate of 40%[4] one-year fatality of more than 50%.[2] With only 20% of patients independent at six months,[2] ICH creates a heavy financial burden as well. Recent studies show that initial hospital costs for ICH average $28,360 with another $16,035 first year post-discharge costs.[5] With such devastating effects, it is important to monitor and manage the modifiable risk factors such as hypertension and lifestyle choices of smoking, cocaine, and excessive use of alcohol. Small vessel diseases related to cerebral amyloid angiopathy (CAA) and hypertension (HTN) are the most common etiologies of non-traumatic ICH, and other manifestations of these pathologies such as leukoaraiosis and sulcal siderosis should be included in a patient's risk profile.

Antithrombotic therapies commonly used in cardiovascular risk management increase the risk of ICH.[6] While their benefit is substantial, the incidence of anticoagulant-associated ICH has quintupled with warfarin use for non-valvular atrial fibrillation[7, 8] and mortality is increased due to a higher rate of hematoma expansion.[9] Magnetic resonance imaging (MRI) evidence of cerebral microbleeds [Figure 1B], small (≤ 5-10 mm diameter) hemosiderin deposits detected on T2*-weighted gradient-recalled echo (GRE) sequences, are associated with cerebral small vessel disease.[3,10] and an increased risk of anticoagulant-related ICH,[11-14] This article will address the available data on imaging and clinical markers of increased ICH risk to guide clinicians on antithrombotic therapy recommendations. We will first define the major etiological categories of ICH and review the evidence on use of antithrombotics in patients who had macrobleeds caused by specific pathologies. We will then review evidence on microbleeds and other imaging markers of increased hemorrhagic risk with a focus on their usefulness in patients without macrobleeds.

CAUSES OF INTRACEREBRAL HEMORRHAGE

Understanding the cause of ICH guides treatment of potentially correctable lesions and helps stratify the risk of recurrent bleeding as they have intrinsically different risks of recurrent hemorrhage. The primary imaging modalities are CT, typically used to diagnose acute ICH [Figure 1A] and MRI to evaluate for underlying vascular malformations or tumor or support a diagnosis of CAA [Figure 1B]. Vascular imaging with MR angiography (MRA) and CT angiography (CTA) are often used and cerebral angiography is recommended patients under 50 years of age, after IVH, when MRI is suspicious for an underlying pathology or does not support a diagnosis of CAA.[2] Repeat brain imaging may be performed after several months to reevaluate for any pathology that may be obscured by the initial bleed or edema. When appropriate imaging does not identify a gross structural or vascular pathology in older adults, the ICH is most commonly attributed hypertension or cerebral amyloid angiopathy.

CEREBRAL AMYLOID ANGIOPATHY-RELATED ICH

Cerebral amyloid angiopathy is commonly found in the elderly and affects the small vessels by the accumulation of amyloid beta-peptides in cortical and leptomeningeal vessel walls.[15] The accumulation causes weakening of vessel walls resulting in hemorrhage or infarction.[16-18] and is also an important cause of cognitive impairment through ischemic and hemorrhagic mechanisms.[19,20] Cerebral microbleeds (CMB) are commonly found in lobar white and gray matter in patients with CAA. Longitudinal studies show that the risk of recurrent ICH in patients with CAA is increased with higher number of microbleeds making CMB an important risk predictor in this context.[21] A definite diagnosis of CAA can only be made upon postmortem examination, but guidelines for diagnosis of CAA in the living are established in the modified Boston Criteria. ch define Probable CAA is defined as the presence of multiple hemorrhages restricted to the cortical or cortico-subcortical regions or a single lobar cortical or cortico-subcortical hemorrhage with either lobar microbleeds and/or disseminated superficial siderosis as detected by CT or MRI in patients ≥ 55 years.[22-24]

Lobar microbleeds detected by T2* GRE MRI thus both contribute to the diagnosis of CAA and predict the occurrence of future ICHs. While lobar hemorrhages might be associated with better long-term functional outcome compared to hemorrhages in the basal ganglia or thalamus[25] the risk of lobar ICH recurrence is significantly higher in CAA patients.[11,13] A study of fifty-nine patients with warfarin-related lobar hemorrhages showed that CAA was an important contributor to anticoagulant-related hemorrhage, even in context of a well-controlled international normalized ratio.[26] There currently is no direct treatment for CAA but adequate control of hypertension is likely to provide protection against all types of ICH including CAA.[27]

HYPERTENSIVE INTRACEREBRAL HEMORRHAGE

Hypertensive small vessel disease is the most frequent cause of ICH.[28, 29] resulting in hemorrhages in deep brain regions, such as the thalamus or basal ganglia.[14] Hypertension is also a major risk factor for ischemic events, and both prior ischemic events and markers of ischemic injury such as white matter hyperintensities, or leukoaraiosis, increase the risk of ICH. [30, 31] The severity of leukoaraiosis correlates with both CAA and hypertensive microvasculopathy and is recognized as a strong risk factor for warfarin-related ICH in both lobar and deep brain locations.[18,32]

Antithrombotic Use in ICH Survivors

CAA-Related ICH

The risk of recurrent ICH in patients with past CAA-related ICH who are not taking antithrombotic therapies is approximately 10%; antithrombotic therapy increases the risk of and severity and poor outcome of the ICH.[14,36] A decision analysis based on a 69-year-old man with a history of ICH and newly diagnosed nonvalvular atrial fibrillation suggested survivors of lobar ICH should not be anticoagulated with warfarin.[14] When case scenarios with different thromboembolic and hemorrhagic risk were reviewed, the superiority of “do not anticoagulate” for lobar ICH survivors remained constant for nonvalvular atrial fibrillation. Although the recently approved newer anticoagulants (dabigatran, rivaroxaban, apixaban) have all shown lower ICH risk when compared to warfarin in phase III trials, [37-39] it remains unclear whether they will tip the risk-to-benefit balance in favor of their use.

Surgical or catheter-based alternatives to long-term anticoagulation in patients with non-valvular atrial fibrillation could be preferred for patients at high risk for ICH.[41,42, 40]

Antiplatelet agents were not associated with an increased risk of ICH recurrence in 27 patients of 127 survivors of lobar ICH (hazard ratio [HR] 0.8, 95% CI 0.3 to 2.3, p=0.73).[43] However, an increased risk of ICH has been seen with aspirin use in patients with CAA-related lobar ICH and higher numbers of cerebral lobar.[36] Aspirin and other antiplatelet use should be considered cautiously and avoided in those at low risk of thromboembolic events, such as in primary prevention.[14,43]

Hypertensive ICH

Antiplatelet treatment was not associated with higher risk of ICH recurrence in survivors of deep hypertensive ICH (HR 1.2, 95% CI 0.1 to 14.3, p=0.88) in an observational follow up study.[43] Anticoagulation after hypertensive ICH might carry a lower hemorrhagic risk than after lobar hemorrhage, but currently should not be recommended unless the risk of an ischemic stroke is very high. Since aspirin carries a smaller risk of bleeding than warfarin, it may be an option for patients with an intermediate risk of ischemia.[14] Similar to the case of lobar ICH, the role of the newer anticoagulants and mechanical approaches in prevention of cardioembolism in patients with non-valvular atrial fibrillation remain to be determined in

survivors of deep hypertensive ICH. Other than avoidance of antithrombotics whenever possible, the best prevention of hypertensive ICH is control of hypertension and reduction of other modifiable risk factors, such as moderate-heavy alcohol consumption.[27,44]

Arteriovenous Malformation and Aneurysm-Related ICH

Recent reviews have not indicated increased risks of bleeding after successful treatment of vascular malformations,[45] but there are no data testing the safety of antithrombotic medications in these patients and it is possible for aneurysms or AVMs to recur following treatment. In the absence of good data, a consultation with a vascular neurologist/ surgeon/ interventionalist is appropriate to participate in decision-making and longitudinal follow up.

Assessing Risks of First-Time ICH

With the development of higher-quality imaging techniques and rapid increase in advanced imaging-based research over the past decades, new radiologic markers have been emerged with the potential to identify people at high risk of first ICH. Among them, cerebral microbleeds have become relatively common incidental findings on MRI scans obtained for other indications.

Clinical Factors

The small vessel pathologies that result in ICH often manifest with their ischemic consequences as cognitive and gait impairments in older adults. There is an overlap between Vascular dementia and Alzheimer's disease,[46] but Alzheimer's disease itself is not a strong risk factor for cerebral hemorrhage and should not be viewed as a contraindication for antithrombotic therapy In vascular dementia, the imaging features discussed below can help make a determination of the prevailing pathology and estimating the hemorrhage risk.

Neuroimaging Findings

In the 1980s, MRI findings of white matter changes, or leukoaraiosis, were commonly identified in older adults and were variously interpreted as Binswanger's disease or as being "non-specific" or "incidental". Leukoaraiosis has proved to be a strong marker of the severity of underlying small vessel disease whereas microbleeds and sulcal siderosis are markers of bleeding prone microvasculopathy.

Cerebral Microbleeds—CMBs [Figure 1B] in the absence of ICH are highly prevalent in the elderly, observed in approximately 15.3% of community-dwelling adults age 45 and older and 35.7% for people 80 years and older.[12] The location of CMBs appears to reflect the type of microvasculopathy; deep CMBs are associated with hypertensive vascular pathology and strictly lobar CMBs with CAA-related small vessel disease.[48] Microbleeds may be indicative of more bleeding-prone areas since the presence of CMB are also associated with ICH[49] and higher risk of mortality for patients with more than 5 CMB.[11] In a cross-sectional matched cohort analysis, the presence of microbleeds was more commonly found in patients with warfarin-related ICH when compared to anticoagulated patients without ICH.[50] Cerebral microbleeds are also markers of progression in cerebral amyloid angiopathy, as CAA patients with higher numbers of microbleeds at baseline experience higher rates of future hemorrhages.[3,21] The strong association of CMB with age, CAA, and warfarin-related ICH make them important features for hemorrhagic risk assessment in older patients.

It remains unclear whether the presence of CMBs without a history of ICH confers sufficient risk of future ICH to tip clinical decisions towards or away from antithrombotic treatment. A Markov decision model suggested, for example, that a risk factor would need to increase the

risk of ICH approximately 13-fold to balance the known benefits of warfarin for preventing atrial fibrillation-related stroke. To date, only one study has compared incident risk of symptomatic ICH in patients who presented with lobar microbleeds without ICH to patients who presented with CAA-related lobar ICH.[51] Cox regression analysis showed no statistically significant difference in incident ICH despite a trend for lower risk in microbleed-only (4.9 per 100 person years) versus the lobar ICH cohorts (8.3 per 100 person-years, $p>0.05$). Patients with lobar microbleeds had a risk of ICH that was not trivial. The use of warfarin in a small number of patients in the microbleed only group was a significant predictor of occurrence of ICH ($p<0.05$) whereas the use of aspirin was not associated with increased risk ($p>0.5$). [51] Further studies are needed to help establish the relationship between the presence of microbleeds and risk of incident ICH and how such risk is modulated by antithrombotic use, especially in community dwelling older people without history of ICH or symptoms.

Cerebral microbleeds have also been implicated as lesions contributing to neurologic dysfunction, as they could directly affect surrounding tissue causing functional or cognitive disabilities. One community based study showed that patients with numerous CMBs performed worse on neuropsychological tests than those without microbleeds.[52] The significance and implications of CMB are important areas of ongoing research efforts.

White Matter Disease (Leukoaraiosis)—White matter disease is common in CAA as well as hemorrhage-prone hypertensive small vessel disease and currently there is no way to distinguish the underlying pathology from imaging characteristics (55,56). A cross sectional study showed that patients with white matter disease taking anticoagulants were at a higher risk for ICH, which increased with severity of leukoaraiosis, even when INR was within target therapeutic limits.[32] Studies indicate that higher white matter disease burden, even without anticoagulants, predicts risk of lobar hemorrhage possibly due to CAA.[53,54] One study found that white matter disease severity correlated with cognitive impairment before occurrence of first lobar intracerebral hemorrhage.[53] Leukoaraiosis patterns have been associated with specific risk factors, such as gender, hypertension and smoking, but further data are needed to determine patterns associated with different neuropathologies.[57] At the present time, mere presence or severity of leukoaraiosis should not be seen as an absolute contraindication for antithrombotic use but the adverse implications of both potential underlying pathologies (CAA and hypertensive small vessel disease) and the commonly co-existing clinical problems such as cognitive impairment and fall risk should all be considered before recommending antiplatelet or anticoagulant medications.

Sulcal (Superficial) Siderosis—Sulcal siderosis [Figure 1B] is caused by focal subarachnoid hemorrhages and may also signal risk for future ICH.[58,59] Case studies have reported the presence of sulcal siderosis concurrent with CAA pathology.[60] A retrospective analysis of T2*-weighted MRIs of patients with histopathologically diagnosed CAA found that sulcal siderosis was present in 23 of 38 CAA cases but none of 22 control patients with histopathologically proven non-CAA ICH.[24] This finding led to the development of the modified Boston Criteria, which now considers presence of focal or disseminated superficial siderosis as a criterion similar to presence of lobar microbleeds.[24] MRI imaging that includes GRE or SWI sequences are optimal to identify sulcal siderosis, micro- and macrobleeds but the meaning and impact of these markers are under investigation.

Future Directions: Genetics and PET Imaging—The Apolipoprotein E (APOE) presents a genetic polymorphism that is relatively common in CAA, determined by three alleles APOE ε2, APOE ε3, APOE ε4. Patients carrying APOE ε2 and APOE ε4 alleles are at greater risk of CAA-related ICH than those with only the common APOE ε3.[61-64] If these

markers were shown to predict ICH risk, then genetic screening could be a useful tool for guiding antithrombotic therapy for patients at risk for vascular events. [65]

Another promising area of imaging research is in the use of noninvasive amyloid imaging with PET agents such as Pittsburg compound B (PiB)[66] to detect the early stages of cerebral amyloid angiopathy.[67] Recent studies have shown that CAA-related hemorrhages occur at sites of high baseline amyloid deposition that can be detected using PiB-PET imaging.[68] Brain amyloid imaging is still an area of active research, but could be a very promising tool for assessing hemorrhage risk associated with CAA.

CONCLUSION

Cerebral macrobleeds and microbleeds originate from different small vessel pathologies that have distinct prognostic significance and management strategies. These lesions, in context with other clinical, imaging and laboratory findings, are helpful in predicting the risk of future intracerebral hemorrhage and guiding antithrombotic therapy recommendations. The current data do not support routine neuroimaging before starting antithrombotics in patients who are otherwise at low risk of ICH, but more research is needed to incorporate this data into a thorough hemorrhagic risk. Warfarin should not be used for non-valvular atrial fibrillation in survivors of CAA-related lobar ICH.

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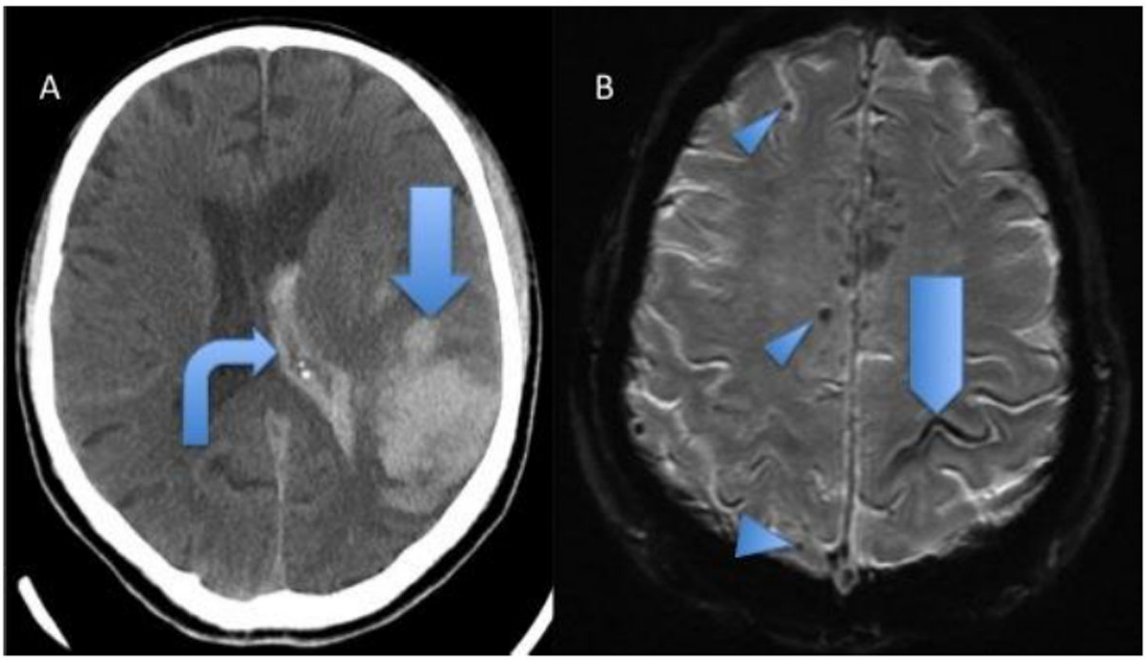

Figure 1.
Hemorrhagic findings of 2 patients with pathologically proven cerebral amyloid angiopathy. **A**, Head CT showing acute lobar parenchymal macrobleed (*arrow*) and intraventricular hemorrhage (*bent arrow*). **B**, GRE MRI shows lobar microbleeds (*arrowheads*) and sulcal siderosis (*pentagon*).