Managing Risk after Intracerebral Hemorrhage in Concomitant Atrial Fibrillation and Cerebral Amyloid Angiopathy.

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Case Description:

A 77 year-old right-handed functionally-independent man presented after waking with a right-sided frontal headache, associated with three episodes of vomiting. His headache progressed over the following twenty minutes, prompting presentation to the Emergency Department. He reported an unsteady gait, but no focal weakness or sensory disturbance. He was known to be in atrial fibrillation (AF), for which he was anticoagulated with warfarin. His other comorbidities included a previous pulmonary embolus, hypertension, and benign prostatic hypertrophy.

On examination, there was no focal neurological deficit and his Glasgow Coma Scale was 15. In view of his severe headache whilst therapeutically anticoagulated, he was investigated with an urgent computed tomography (CT) scan of his head. This demonstrated a 58 by 37 mm right temporal lobe hemorrhage (figure 1). His international normalized ratio (INR) on admission was 2.13, which was corrected with vitamin K and prothrombin complex. The hemorrhage was managed conservatively with blood pressure control, initially requiring a labetalol infusion followed by oral lisinopril and doxazosin.

He remained neurologically stable throughout his admission. He was discharged 14 days later with a minor deficit in short-term memory but no other focal neurological deficit. His modified Rankin score was one. In view of the acute hemorrhage, anticoagulation was withheld as further hemorrhagic risk was deemed to outweigh antithrombotic benefit.

Magnetic resonance imaging (MRI) was performed one month after discharge and demonstrated evolution of the hematoma (figures 2a and 2b). Gradient echo images also demonstrated a small right parietal lobe hemorrhage (figure 2c). These findings were suggestive of cerebral amyloid angiopathy (CAA) as the etiology of his presenting right temporal lobe hemorrhage.

In view of the findings suggestive of CAA, it was felt that the risks of recurrent bleeding with long-term anticoagulation outweighed the benefits of stroke risk-reduction from AF-related thromboembolism. He was therefore referred to the regional cardiothoracic centre for consideration for a left atrial appendage closure.

Discussion:

This case highlights the management challenge in balancing the ischemic stroke risk from AF against the recurrent hemorrhagic stroke risk from CAA following an intracerebral hemorrhage. The prevalence of CAA increases with age, and was identified in 57% of patients aged over 59 years in one autopsy study.[1] Consequently, a large cohort in the general population will have concomitant AF and CAA, though the latter may be undetected unless gradient echo MRI is performed. CAA is a common cause of intracerebral hemorrhage in patients over 60 years of age, and it has been reported to underly 12-20% of intracerebral hemorrhages in two large retrospective studies.[2,3] In contrast to intracerebral hemorrhages of hypertensive etiology, which tend to occur in subcortical areas, hemorrhages secondary to CAA tend to occur in the cerebral cortex and display a lobar pattern.[4] Histopathological

confirmation is required to make a definitive diagnosis of CAA, but the presence of lobar intracerebral hemorrhage on non-contrast CT, or multiple cortical microhemorrhages on gradient echo MRI in a patient older than 55 years of age, is highly suggestive for CAA.[4] The differential diagnosis of CAA can be further supported by the modified Boston criteria, which incorporates criteria including age, neuro-imaging findings, and post-mortem histology to offer a high sensitivity and specificity in the diagnosis of CAA.

The risk of cardioembolic stroke from AF is well-recognized and is influenced by the presence of comorbidities such as congestive cardiac failure, diabetes mellitus, previous stroke, and hypertension. The attributable risk of stroke for individuals with AF increases with age, rising from 1.5% for patients in their sixth decade, to 23.5% in the ninth decade.[5] In the absence of contraindications, anticoagulation with warfarin or a direct oral anticoagulant (either a direct thrombin inhibitor or a factor Xa inhibitor) is used to reduce the risk of cardioembolic ischemic stroke secondary to AF, and is recommended in men with a CHA_2DS_2-VASc score $\geq$1 and in women with a CHA_2DS_2-VASc score of $\geq$2.[6]

In patients who have had an intracerebral hemorrhage with co-existing AF and CAA, the risk of ischemic stroke without anticoagulation must be carefully considered against the risks of recurrent intracerebral hemorrhage exacerbated by anticoagulation. A decision-analysis model for the use of warfarin in AF in the setting of a previous intracerebral hemorrhage suggests that the risks associated with warfarin outweigh the benefits, particularly when comparing lobar to deep intracerebral hemorrhage; the withholding of warfarin resulting in an increase in quality-adjusted life expectancy by 1.9 and 0.3 quality-adjusted life years respectively.[7] The estimated risk of recurrent intracerebral hemorrhage in CAA varies, with a

review by Poon et al. estimating that the risk of recurrent hemorrhage for lobar hemorrhages after 1 year to be between 2.5-28.2%, compared to a lower risk of 1.3-10.6% in non-lobar hemorrhage.[8] There are currently no guidelines on anticoagulant use in the setting of AF following intracerebral hermorrhage secondary to concomitant CAA. Consequently, management of such patients remains a challenge. The HAS-BLED score is not validated for use in CAA so risk stratification must be based on the aforementioned recurrence rates balanced against the CHA_2DS_2-VASc score. In the case of our patient, his CHA_2DS_2-VASc score was 5, giving him an adjusted ischemic stroke risk of 6.7% per annum, whilst the pooled results from Poon et al. would suggest that the rate of lobar hemorrhage reccurrence for those not taking anticoagulation exceeds this ischemic stroke risk even before the additional hemorrhagic risk from anticoagulation is considered.[8]

The recurrence rate of intracerebral hemorrhage in CAA secondary to antiplatelet use is also unclear, largely due to randomized clinical trials often excluding patients with previous intracerebral hemorrhage in trials of antithrombotics. Longitudinal observational cohort studies (typically single centre studies of small numbers) have shown conflicting results for recurrence of lobar hemorrhage for individuals taking antiplatelet medication. This, coupled with the lack of efficacy for aspirin preventing stroke in patients with AF, casts uncertainty on the role of antithrombotic agents in concomitant AF and CAA.[6] Further research and meta-analysis into this area is required, and a Cochrane Library review is currently in progress.

In view of the inherent bleeding risk associated with anticoagulation in AF, there has been much interest in non-pharmacological methods for reducing thromboembolic stroke risk. The

left atrial appendage has been shown to be the source of thromboemboli in 90% of patients with non-valvular AF, and excluding the left atrial appendage from the systemic circulation has been investigated to reduce the risk of cardio-embolism.[9] Percuteneously implanted closure devices can be used to achieve this, potentially offering an avenue to reduce the risk of thromboembolism secondary to AF, whilst avoiding the risks of anticoagulation-associated intracerebral hemorrhage. Left atrial appendage closure was shown to be at least non-inferior to anticoagulation with a relative risk of stroke, cardiovascular death, and systemic embolization of 0.62 (95% CI 0.35-1.25) for the intervention versus anticoagulation group.[9] It should be noted that in this study, patients remained on warfarin until closure of the left atrial appendage was confirmed on trans-oesophageal echocardiogram, and the safety in patients in whom anticoagulation is contraindicated is yet to be fully determined. More recently, the procedure itself has been shown to be feasible and safe in individuals with concomitant AF and previous intracerebral hemorrage who received peri-procedural heparin, though such studies did not discrimate hemorrhages by etiology.[10] A further small study has suggested that left atrial appendage closure can be performed safely and effectively with antithrombotic agent cover rather than anticoagulation but the safety of antithrombotic agents in CAA also remains uncertain.[11] Superiority of either left atrial appendage closure or longterm anticoagulation requires further study, though is difficult to demonstrate due to low event rates in each treatment arm. Nevertheless, as the facility for left atrial appendage closure becomes increasingly available, it may provide a safe alternative strategy for stroke risk-reduction for patients with AF complicated with other bleeding risks.

Balancing the risk of ischemic stroke and hemorrhagic stroke in patients with co-existing AF and CAA remains a challenging area, and requires careful consideration on a case-by-case basis. Guideline development requires a greater understanding of the safety of anticoagulant

and antithrombotic drugs in these patients, and of the safety of left atrial appendage exclusion procedures without the concomitant use of these agents. Future research and clinical management must consider the underlying etiology of the hemorrhage for risk prediction to guide treatment.

Take-Home Points

- Cerebral amyloid angiopathy is difficult to diagnose definitively, but may be suspected based on imaging findings of lobar intracerebral hemorrhage on non-contrast CT or microhemorrhages on gradient echo MRI.

- There is a high risk of recurrent hemorrhage in patients with intracerebral hemorrhage secondary to cerebral amyloid angiopathy, above that expected with non-lobar hemorrhages.

- Anticoagulant and antithrombotic agents should be avoided in the setting of cerebral amyloid angiopathy unless the risk of ischemic stroke outweighs the high risk of hemorrhagic stroke.

- Left atrial appendage closure may provide a safe alternative for reducing the risk of ischemic stroke in atrial fibrillation for individuals where anticoagulation is contraindicated.

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None.

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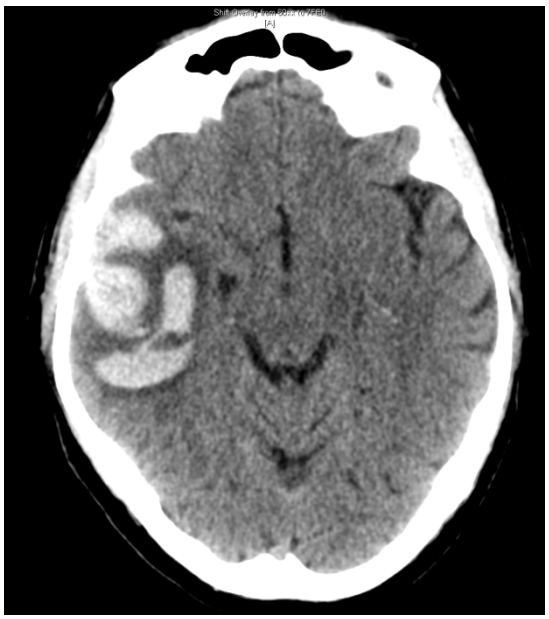

Figure 1. Non-contrast axial CT head showing a right temporal lobe intracerebral hemorrhage (maximum diameter 58 x 37 mm) and associated mass effect with sulcal effacement.

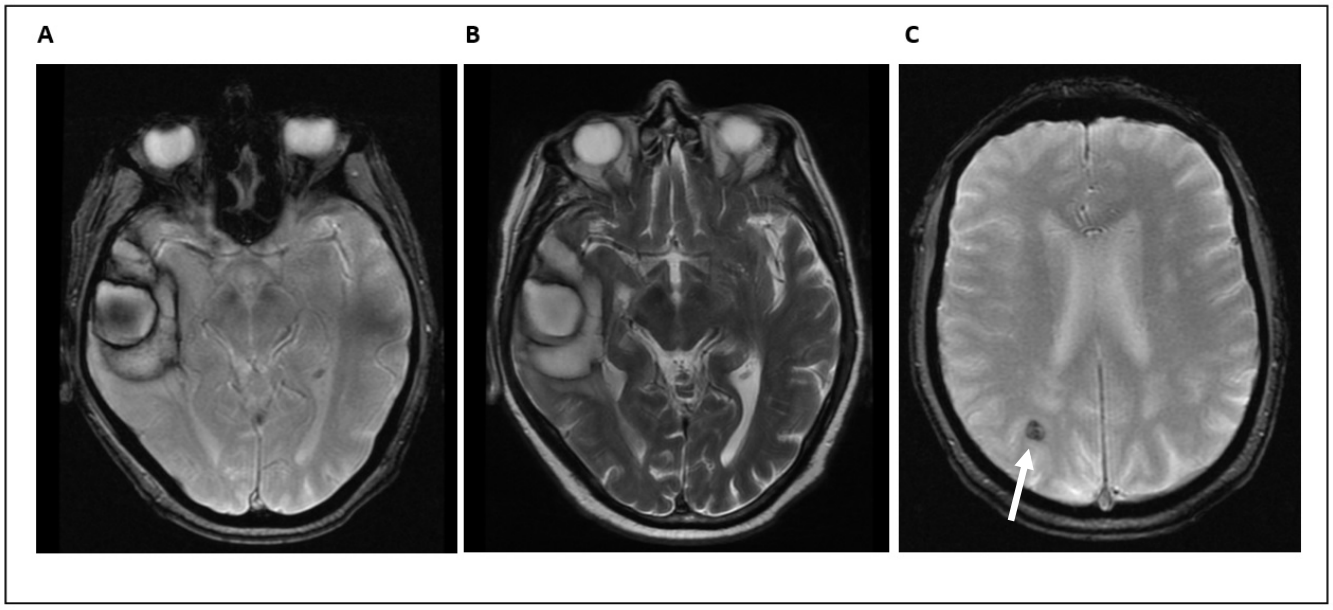

Figure 2. MRI head performed one month following intracerebral hemorrhage. **A**, Gradient echo and **B**, T2-weighted MRI showing evolution of the hemorrhage, with low intensity peripherally, indicating hemosiderin formation. **C**, Gradient echo demonstrating an additional 8mm focal right parietal hemorrhage (arrow).