

Cerebral Amyloid Angiopathy: An Important Differential Diagnosis of Stroke in the Elderly

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Abstract

Cerebral amyloid angiopathy (CAA) accounts for approximately 10–20% of spontaneous intracerebral haemorrhage (ICH). This figure is thought to be higher in the elderly population. With the increasing life expectancy of our population, we anticipate that the prevalence of CAA-related ICH will increase in tandem. Although CAA-related ICH and hypertension-related ICH are distinct entities based on histopathology and imaging, the clinical presentation of the two conditions is similar. The use of brain computed tomography (CT) scans remain the ICH imaging modality of choice in Malaysia due to its availability, cost, and sensitivity in detecting acute bleeds. On the other hand, the use of brain magnetic resonance imaging (MRI) with susceptibility-weighted imaging (SWI) sequencing enables the clinician to determine the presence of chronic blood products in the brain, especially clinically silent microbleeds associated with CAA. However, the use of brain MRI scans in our country is limited and leads to a blurring of lines when differentiating between hypertension-related ICH and CAA-related ICH. How this misrepresentation affects the management of these conditions is unclear. In this study, we present two cases of ICH to illustrate this point and to serve as a springboard to question current practice and promote discussion.

Keywords: cerebral amyloid angiopathy, stroke, intracerebral haemorrhage, magnetic resonance imaging

Introduction

Cerebral amyloid angiopathy (CAA) is characterised by deposition of amyloid β -protein (A β) within the walls of medium and small-sized arteries in the cerebral cortex and leptomeninges (1). This leads to increased vascular fragility and predisposes to rupture of the blood vessel. It is estimated that 10% of intracerebral haemorrhage (ICH) is exclusively due to cerebral amyloid angiopathy haemorrhage (CAAH) (2).

Imaging plays an important role in the diagnosis of ICH. On brain computed tomography (CT) scans, acute bleeds appear as defined, hyperdense lesions with variable perilesional oedema. CAAH tends to be superficial (cortical–subcortical junction) and limited to the cortex, sparing the deep white matter and brain stem; there also may be associated subarachnoid or subdural haemorrhage (3). In contrast, deep lobar haemorrhage, which is most commonly associated with chronic hypertension, classically occurs in the basal ganglia, thalamus, cerebellum, or brain stem, and tends to be large, with mass effect and intraventricular extension (4).

Occasionally, CAAH can be large and situated in areas of the brain more associated with hypertensive bleeds. In such cases, CT is less sensitive at differentiating between the two. Magnetic resonance imaging (MRI) of the brain with susceptibility-weighted imaging (SWI) sequencing allows better differentiation, as it detects hemosiderin deposits present in acute and chronic bleeds typical of CAAH. Currently, CAAH is diagnosed by brain imaging using the Boston criteria (5).

We present two cases of ICH that demonstrate how MRI was used to distinguish between CAAH and deep lobar haemorrhage when patients presented in a clinically atypical fashion. In both cases, CT was used to make the initial diagnosis. However, the initial diagnosis of CAAH was missed in one patient due to the atypical site and size of the lesion. The patient was initially diagnosed with ICH secondary to hypertension, and the diagnosis was only revised based on a later MRI. Current management guidelines do not distinguish between CAAH and deep lobar haemorrhage with respect to secondary prevention.

Case Report

Case 1

A 78-year-old woman presented with sudden left hemiparesis associated with left facial asymmetry and slurred speech. On arrival to the emergency department, she developed an episode of generalised tonic-clonic seizure that lasted for five minutes. Her blood pressure was 168/90 mmHg and her pulse rate was 78 beats per minute with regular rhythm. Her Glasgow Coma Scale (GCS) was 13/15 (E4V4M5), with reduced power over the left upper and lower limbs (grade 3/5). There was an upper motor neuron palsy of the VIIth cranial nerve on the same side. No other abnormalities were apparent during the physical examination. The patient's next of kin reported that she had a history of high blood pressure but had stopped taking her medication. There was no evidence of cognitive dysfunction from the collateral history.

A brain CT scan showed an acute right frontal ICH involving the precentral gyrus with small subdural extension (Figure 1a), suggestive of CAAH. A brain MRI was performed on the subject as an inpatient, and it revealed global atrophy, with microbleeds located in the cortical-subcortical locations in the cerebrum (Figure 1b). These were only seen on susceptibility-weighted imaging (SWI) sequence, with sparing of the deep grey matter and cerebellum. There were associated confluent hyperintense white matter lesions on T2-weighted image consistent with leukoencephalopathy and global cerebral atrophy. A diagnosis of possible CAAH was made based on the brain MRI findings.

She was empirically started on an anti-epileptic drug and was discharged nine days later with good neurological recovery; she was also seizure-free. Her blood pressure remained within normal limits during her hospital stay and she was advised to monitor her blood pressure at the nearest clinic.

Case 2

A 66-year-old woman was brought to the hospital with a reduced level of consciousness and right hemiparesis. She had a history of hypertension and diabetes mellitus. Her blood pressure was 180/90 mmHg with a regular pulse rate of 72 beats per minute. She had a reduced conscious level with a GCS of 10/15 (E3V3M4) and a marked reduction in the power of the right upper and lower limbs, corresponding to grade 3/5.

Brain CT scan revealed a large ICH in the left frontal lobe with intra-ventricular extension (Figure 2a). CT angiography showed no intracranial aneurysm or intracerebral vascular malformation. A diagnosis of deep lobar haemorrhage due to chronic hypertension was made. An emergency insertion of an external ventricular drain (EVD) was performed on the day of admission, but it was removed ten days later after becoming infected. Serial brain CT scans showed stable, mild hydrocephalus with resorption of the intraventricular blood and reduction in the size of the left frontal haematoma. The patient did not have a brain MRI during this admission. She was discharged after a 15 days

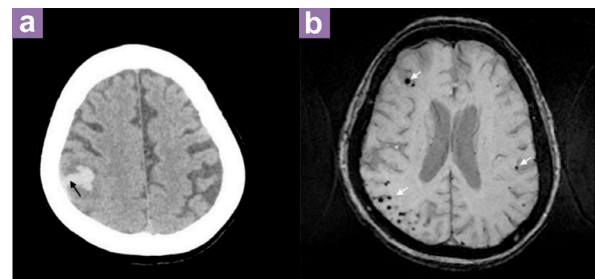


Figure 1: CT scan (a) showing acute intracerebral haemorrhage in the right frontal lobe with subdural extension (black arrow). MRI susceptibility weighted imaging (SWI) image (b) revealed other foci of microhaemorrhages in the cortical-subcortical region (arrows).

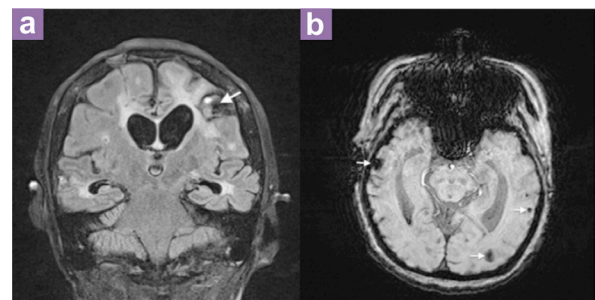


Figure 2: Fluid attenuated inversion recovery (FLAIR) sequence (a), showing the lobar hemorrhage in the left frontal lobe (arrow) with intraventricular extension (not shown). The SWI image (b) reveal multiple other cortical-subcortical macro- and microhaemorrhages (arrows).

stay.

Two months later she was re-admitted for seizures attributed to gliosis secondary to the left frontal haemorrhage. On further assessment, the family reported that she had cognitive dysfunction that predated her first hospital admission. A brain MRI was performed, which revealed multiple microhaemorrhages in a cortical–subcortical distribution (Figure 2b). On account of the new findings, the diagnosis was revised to possible CAAH, and the patient was subsequently discharged with antiepileptic medication.

Discussion

The two cases presented are typical examples of elderly patients with ICH and multiple comorbid illnesses. In both cases, the patients were chronic hypertensives. In the first case, the CT brain revealed a small area of haemorrhage suggestive of CAAH and the subsequent MRI findings supported the diagnosis. In the second case, the size and region of the haemorrhage seen on CT was more suggestive of deep lobar haemorrhage secondary to hypertension. It was only later that the diagnosis was revised to CAAH due to the benefit of the MRI. This to us underlines the importance of an MRI in making a diagnosis of CAAH.

Greater availability of brain CT makes it a first-line imaging tool for stroke patients in most centres. It is a useful tool to diagnose ICH and to exclude other causes, such as ischaemic infarcts and tumours. Lobar haemorrhage in the elderly, even in the presence of hypertension, should raise the suspicion of CAAH. Brain MRI with gradient-echo (GRE) or SWI sequencing is very useful for demonstrating microhaemorrhages in the cortical–subcortical regions in CAAH (3). These findings are usually not demonstrable in CT scans and other conventional MRI sequences.

The Boston criteria were devised to allow a diagnosis of CAAH-related ICH to be made based on clinical and imaging findings. However, the Boston criteria make no distinction between MRI and CT scans for imaging. Knudsen et al. showed that probable CAAH diagnosed by a combination of CT or MRI scan had a sensitivity of 100% against pathologic samples, but the sensitivity rate dropped to 62% in possible CAAH (5). van Rooden et al. were able to show an increase sensitivity rate of 10% in diagnosing CAAH by using MRI with T2* weighted imaging, which was able to detect microbleeds (6). This shows that the sensitivity of the Boston criteria increases when brain MRI scans with sequences capable of

detecting microbleeds are used.

In the two cases presented, atypical features on initial brain CT imaging—i.e. large infarct size, interventricular extension, and history of hypertension made the diagnosis of CAAH less straightforward, despite the presence of lobar haemorrhage. The diagnosis of possible CAAH was only considered following subsequent brain MRI with SWI sequencing that showed the presence of other macro and chronic microbleeds in a cortical–subcortical distribution that spared the deep grey matter and brainstem. The second case especially highlights the limitations of brain CT scans in diagnosing CAAH, especially when there is a history of hypertension.

Presently, there is no evidence-based treatment for CAAH, but that does not mean that the exercise in diagnosing it to a high degree of certainty is purely an academic one (7). Although there are similarities between the two varieties of ICH, there are sufficient differences between them to raise questions regarding management.

It has been shown that the prevalence of ischaemic heart disease in patients with ischaemic stroke is approximately the same as in those with deep lobar haemorrhage (8). Current recommendations advocate the use of aspirin in patients with hypertensive bleeds who are at high risk of future ischaemic stroke or who have evidence of silent ischaemic infarcts on imaging (9).

However, it has also been shown that CAAH has a higher rate of recurrence compared to deep lobar haemorrhage (8). The burden of intracerebral microbleeds, which can only be detected by gradient echo (GRE) or SWI sequence MRI, confers an increased risk of recurrent ICH (10). One would argue that for CAAH, starting aspirin in patients with CAAH could potentially cause more harm than good; however, there are currently no evidence-based guidelines that address this risk. Similarly, to the best of our knowledge, there is no guidance on the use of anticoagulants in patients with CAAH or atrial fibrillation. The issue becomes more pressing with the introduction of novel oral anticoagulants (NOACs) into the market and further highlights the importance of accurately diagnosing CAAH, as it may have an impact on the clinical decision-making process.

Blood pressure control is another management aspect that is contentious. The lowering of blood pressure has been shown to reduce the risk of recurrent lobar haemorrhage (11). Indeed, treating mid-life hypertension reduces the risk of developing vascular cognitive

impairment and Alzheimer's dementia (12). This issue is important as dementia in CAAH is more common than dementia following hypertensive bleed (13). The question of whether the evidence regarding blood pressure control in vascular cognitive impairment and Alzheimer's dementia can be translated for use in dementia with CAAH remains unanswered. To our knowledge, there are currently no well-designed studies that address this issue.

Having an MRI scanner in every hospital would be economically challenging, especially in a developing country such as Malaysia. A more financially feasible alternative is to improve the sensitivity of CT scanning in detecting CAAH, ergo further studies are required that especially relate to the MRI GRE/SWI correlation with CT images in CAAH.

Conclusion

We suggest the use of brain MRI with GRE/SWI sequences in patients with atypical deep lobar haemorrhage. In presumed cases of deep lobar haemorrhage, it is more likely that CAAH might be misdiagnosed if only CT imaging is used. This will impact on secondary preventive measures, especially regarding the use of antiplatelets in this group of patients. This is assumed to be true, as the current body of evidence regarding their use in CAAH does not adequately address these issues. Therefore, more data is required regarding CAAH, beginning with correctly identifying and diagnosing the condition in those at risk.

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Conflict of Interests

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SA, SSO and RS have been involved in the drafting of the manuscript.

SM and RS have been involved in critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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