A SCARLET ENEMY OF THE BRAIN – A PRACTICAL APPROACH TO DIAGNOSIS AND MANAGEMENT OF CEREBRAL AMYLOID ANGIOPATHY

*Sue Yin Lim, Amlyn Evans, Tatiana Mihalova

Department of Clinical Neurology, Queen's Medical Centre, Nottingham, UK
*Correspondence to sue_yin23@yahoo.com

ABSTRACT

We present two cases of elderly patients admitted with neurological dysfunction due to isolated focal cortical subarachnoid bleeding and intracerebral lobar haemorrhage, respectively. We discuss the distinguishing features in their clinical and radiological presentations which led to their diagnosis of probable cerebral amyloid angiopathy (CAA). In the hope of encouraging thoughtful learning, we have designed a series of case-based questions with accompanying answers to explain the investigative pathways and management strategies in suspected cases of CAA.

Keywords: Cerebral amyloid angiopathy, non-aneurysmal subarachnoid haemorrhage, focal cortical subarachnoid haemorrhage, intracerebral haemorrhage.

CASE 1

A 76-year-old retired engineer presented with two episodes of tingling in the left arm accompanied by tonic posturing of his fingers, occurring several days apart. The first attack lasted 30 minutes and was heralded by a 3-hour prodrome of gradually progressive occipital headache. The second episode was shorter in duration, lasting 15 minutes, and occurring in the absence of a headache. His past medical history included asbestos-related pleural plaques and right total hip replacement. He took no regular medication, has never smoked, and has consumed no alcohol. Admission blood pressure was 120/70 mmHg. Neurological examination including fundoscopy was unremarkable. Computed tomography (CT) brain images showed a small acute subarachnoid haemorrhage over the right central sulcus (Figure 1).

Q1: What is the Differential Diagnosis of Subarachnoid Haemorrhage and How Would You Investigate Further?

The majority of subarachnoid haemorrhage is caused by an arterial aneurysmal rupture, with

Figure 1: Non-contrast computed tomography scan showing hyperdensity in the right central sulcus (arrowed) consistent with acute subarachnoid haemorrhage.

Table 1: Causes of subarachnoid haemorrhage with no demonstrable aneurysm on cerebral angiography.[1,2,19]

<u>Most common causes</u>
   <u>Patients ≤60 years old</u>
   • Reversible cerebral vasoconstriction syndrome
   • Posterior reversible encephalopathy syndrome
   <u>Patients ≥60 years old</u>
   • Cerebral amyloid angiopathy

<u>Other causes</u>
   • Cortical/dural venous sinus thrombosis
   • Pial arteriovenous malformation
   • Dural arteriovenous fistulas
   • Arterial dissection
   • High-grade atherosclerotic carotid stenosis
   • Vasculitides (Polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, primary angiitis)
   • Moya-moya disease
   • Infectious/septic aneurysms
   • Cavernomas
   • Cerebral abscesses
   • Coagulopathies, thrombocytopenia (e.g. idiopathic thrombocytopenic purpura)
   • Primary and secondary brain neoplasms
   • Drugs (cocaine, anticoagulants)

an associated mortality rate of up to 50%. Non-aneurysmal bleeding is much less frequent, accounting for 15%[1] of cases, and carries a varied prognosis depending on the underlying cause. Isolated convexity subarachnoid haemorrhage (as seen in case 1) refers to a distinctive pattern of non-aneurysmal bleeding where the extravasated blood is confined to the subarachnoid space over the surface of the cerebral hemisphere. A 5-year retrospective review of 389 cases of spontaneous subarachnoid haemorrhage by Kumar et al.[2] found localised bleeding restricted to the convexity sulci of the brain in 7.45% of patients, suggesting that it is an important subtype of subarachnoid haemorrhage. Cerebral amyloid angiopathy (CAA) appears to be a frequent cause in patients older than 60 years while reversible cerebral vasoconstriction syndrome may be the most prevalent cause in patients under the age of 60 years.[2] Other recognised aetiologies are listed in Table 1.

Our patient underwent cerebral magnetic resonance angiography (MRA) which did not identify any cerebral aneurysm. His T2*-weighted gradient-recalled echo (GRE) MRI brain images (Figure 2), however, revealed multiple cortico-subcortical microhaemorrhages. CAA is therefore postulated to be the probable cause of his subarachnoid bleed.

Catheter angiography was not undertaken as the history and distribution of subarachnoid blood were not suggestive of a high pressure arterial bleeding event from an aneurysm.

Q2: What are the Pathological and Radiological Features of CAA-Related Haemorrhage?

CAA is characterised by the deposition of congophilic amyloid material in the media and adventitia of small-to-medium sized arteries, arterioles, and capillaries in the cerebral cortex and the overlying leptomeninges. Vessels infiltrated by amyloid are fragile and vulnerable to microaneurysm formation, extravasation, and haemorrhage.[3]

• Intracerebral haemorrhage and microbleeds

The lobar haemorrhages and microbleeds of CAA are characteristically cortical or cortico-subcortical in location, and are often multifocal or recurrent. All lobes can be affected, although the occipital cortex tends to be the most frequently and most severely involved.[4] CAA can also affect vessels in the cerebellar region, but in contrast to hypertensive vasculopathy (another common cause of intracerebral haemorrhage), it tends to spare the basal ganglia, thalami, and brainstem.[3]
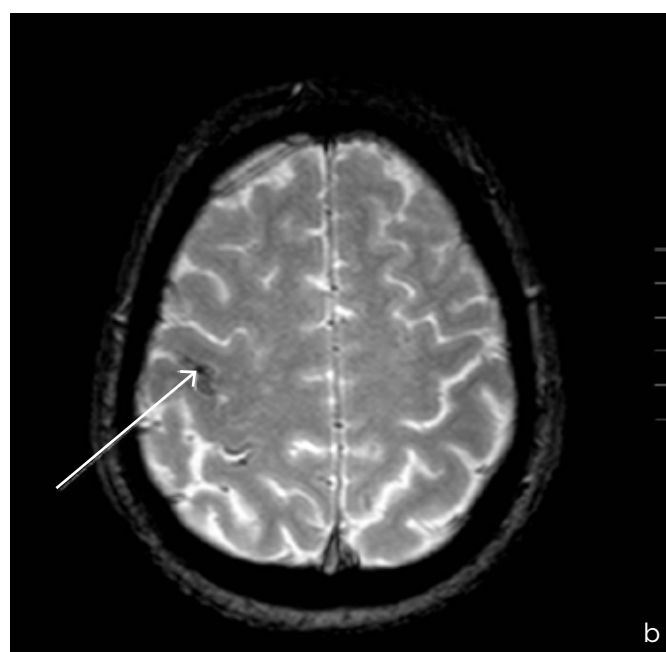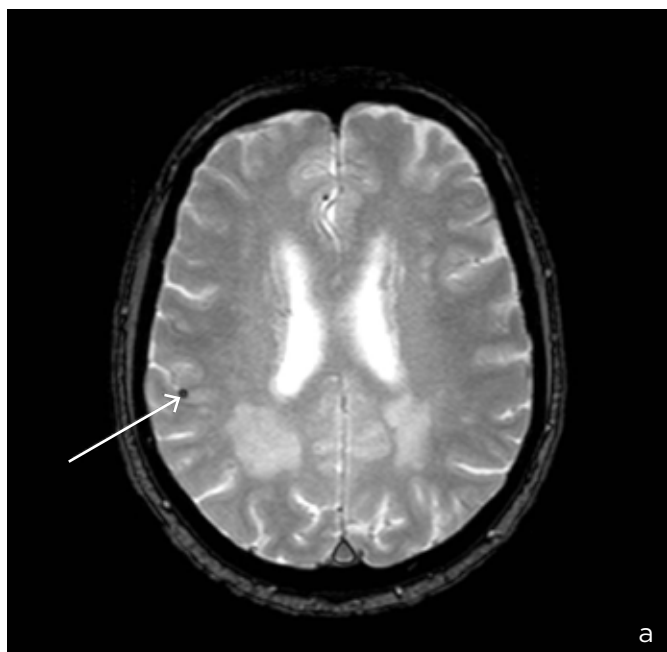
Figure 2: a) Gradient echo T2 scan (T2*) showing a subcortical area of low signal (arrowed) consistent with a small subcortical microhaemorrhage. This is one of several such lesions on the scan; b) another slide from the same study showing the right central sulcus subarachnoid haemorrhage.

• **Convexal subarachnoid haemorrhage**

It is recognised that the lobar haemorrhages of CAA often penetrate into the subarachnoid space causing secondary subarachnoid haemorrhage. Histopathological evidence from more recent autopsy cases have, however, indicated that - at least in some cases - haemorrhage in the cortical subarachnoid space (due to rupture of meningeal vessels) may in fact represent the primary site of bleeding, with or without secondary extension into the underlying brain parenchyma.[3]

• **Cortical superficial siderosis**

Focal or disseminated cortical superficial haemosiderosis (linear residues of blood in the superficial layers of the cortex) is another more recently recognised manifestation of CAA. Although it may, in some cases, represent extension of blood from a previous lobar haemorrhage, the primary mechanism may in fact be repeated leakage from brittle leptomeningeal vessels into the subarachnoid space with resultant haemosiderin deposition in the subpial layers of the brain.[5,6]

• **Choice of imaging**

Although acute intracerebral macrohaemorrhages and acute focal cortical subarachnoid bleeding can be revealed by a cranial CT scan, this imaging modality does not permit the detection of cerebral microbleeds or cortical superficial siderosis, both of which require T2*-weighted GRE MRI sequences for visualisation.[7] Indeed, cortical superficial siderosis and/or cortical-subcortical microbleeds may be the sole imaging indicators of CAA. Susceptibility weighted imaging (SWI) is a new MRI technique which has been reported to be more sensitive than GRE for microbleed detection, although its contribution to diagnostic accuracy and the clinical relevance of identifying different numbers of cerebral microbleeds have not yet been fully established.[4,8]

Q3: What are the Headache Characteristics in Patients with Isolated Convexal Non-Aneurysmal Subarachnoid Haemorrhage, in Comparison to Patients with Aneurysmal Subarachnoid Haemorrhage?

Thunderclap headache is the prototypical symptom of aneurysmal subarachnoid haemorrhage. In contrast, headache is typically absent in patients with isolated convexal non-aneurysmal subarachnoid haemorrhage due to CAA.[9] When headache is present, patients may report non-specific cephalalgia or complain of symptoms mimicking migraine with aura.

Some patients with convexal subarachnoid haemorrhage do present with an explosive onset severe headache akin to aneurysmal rupture, mostly in those with reversible cerebral vasoconstriction syndrome.[10]

Q4: What are the Recognised Clinical Manifestations of CAA?

• Amyloid spells

Transient focal neurological episodes in patients with CAA can be recurrent and stereotyped, sometimes termed 'amyloid spells'.[11] Both positive and negative symptoms may occur at equal rates. Positive symptoms may comprise of transient paraesthesia, limb-jerking episodes, and visual complaints such as photopsia or teichopsia. Negative symptoms include focal weakness, numbness, dysphasia, and visual loss. The spells are typically brief, usually lasting <10 minutes with up to 70% terminating under 30 minutes.[11]

Amyloid spells appear to be anatomically correlated with haemorrhagic lesions, i.e. the phenomenology of the spells corresponds to the cortical location of blood/haemosiderin.[11] The exact mechanism for these spells is not known. One postulated theory is focal seizure activity. Certainly, there are reports indicating either cessation or frequency reduction of amyloid spells following treatment with antiepileptic drugs. An alternative mechanism that has also been suggested is cortical spreading depression, triggered by the presence of blood/haemosiderin in the subarachnoid space and the superficial cortical layers.[12]

Of note, cortical superficial siderosis and/or focal cortical subarachnoid bleeds (which are thought to be primarily responsible for amyloid spells) may represent a warning sign for future intracranial haemorrhage. A study[13] of 51 patients with superficial siderosis found that almost half of these patients went on to develop new intracranial haemorrhagic events during a median follow-up period of 35 months. This is of important clinical significance as amyloid spells presenting with negative symptoms can masquerade as transient ischaemic attacks, prompting the initiation of antiplatelet agents which could further increase the risk of haemorrhage from CAA.

• Cognitive impairment and dementia

There are several mechanisms which may underlie intellectual impairment in patients with CAA. White matter leukoaraiosis is one such mechanism, giving rise to subcortical dementia over weeks to months.[3] A possible explanation for this leukoencephalopathy is chronic hypoperfusion of the periventricular white matter from diffuse amyloid-related narrowing or occlusion of cortical penetrating vessels. Other mechanisms that are likely to contribute include lobar macro and microhaemorrhages, as well as the cumulative effect of 'silent' ischaemic lesions. Two recent studies[14,15] have also found a notably greater prevalence of cortical superficial siderosis in cognitively impaired patients when compared to the general population, and its presence appears to be independently associated with lower cognitive scores, cerebral white matter hyperintensities, and microbleeds.

CAA is also found in association with Alzheimer's disease (AD), probably reflecting their closely related pathogenic processes. The vascular amyloid deposits in CAA are primarily composed of a 39-43-amino acid β-amyloid (Aβ) peptide, which is the same constituent of senile plaques in AD although the ratio of Aβ40/Aβ42 is higher in CAA.[3] Both sporadic CAA and AD share a common genetic risk factor – the apolipoprotein E Ɛ4 allele. The apolipoprotein E Ɛ2 allele is also associated with sporadic CAA, but not with AD.[7]

• CAA-related inflammation[7,16]

CAA-related vascular/perivascular inflammation is a rare but potentially reversible disease manifestation. It is thought to represent an immune-mediated inflammatory reaction to the presence of vascular amyloid deposits. The clinical picture consists of subacute, progressive cognitive and neurological dysfunction with a varying combination of focal neurological deficits, headache, seizures, and encephalopathy.

The typical neuroimaging appearance is that of asymmetric white matter lesions (often large and confluent, with or without mass effect) visualised on T2 or FLAIR-weighted MRI images, along with multiple microbleeds seen on gradient echo sequences. The white matter lesions may extend into the cortical grey matter and there may be meningeal or parenchymal enhancement following the administration of gadolinium. Mimics such as acute disseminated encephalomyelitis, progressive multifocal leukoencephalopathy, neurosarcoidosis, and malignancies need to be excluded. A brain biopsy may be necessary to secure the diagnosis.

It is important to recognise CAA-related inflammation as it may respond to immunosuppressive treatment. Responders may follow either a monophasic or relapsing course.

CASE 2:

A 69-year-old gentleman was admitted with a 10-day history of headache, vomiting, and some word-finding difficulties. Examination revealed a right haemianopic visual field defect. He was referred directly to the neurosurgical team following CT head findings of a left-sided irregular haemorrhagic mass lesion in the left occipital lobe (Figure 3). Brain MRI revealed the lesion as being predominantly haemorrhagic in nature with an additional soft tissue component suggestive, but not definitive, of an underlying tumour (Figure 4). CT chest, abdomen, and pelvis showed no radiological evidence of primary malignancy outside the central nervous system. He underwent uneventful surgical debulking of the left occipital mass. Histopathological examination of the excised tissue showed no evidence of tumour but instead identified amyloid deposition in many vessels.
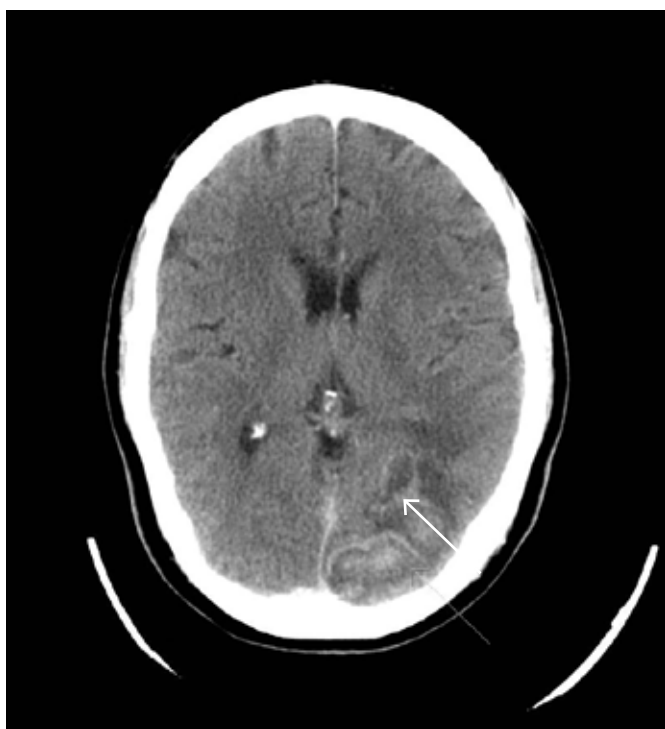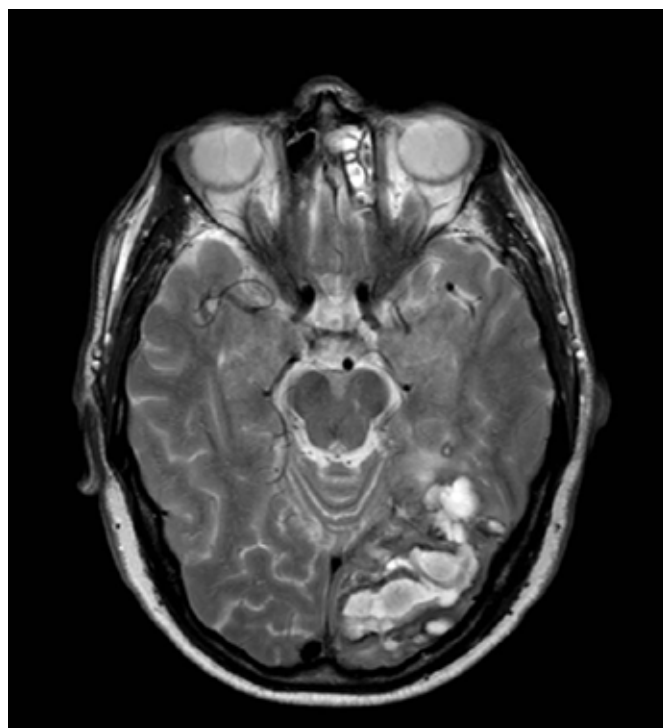

Figure 4: Axial T2 weighted MRI scan showing haemorrhage in the left occipital lobe. Superficial siderosis and distant microhaemorrhages were not seen on T2*-weighted sequences performed post-operatively.

Figure 3: Non-contrast computed tomography scan showing area of irregular haemorrhage in the left occipital lobe (arrowed) with mass effect.

Q5: In What Circumstances Should a Brain Biopsy/Surgical Intervention be Considered?

A brain biopsy in patients with possible or probable CAA will help to strengthen the diagnosis in accordance to the classic and modified Boston diagnostic criteria (Table 2). However, neuropathological examination seldom alters the clinical management, and the risk-benefit balance tends to be against a brain biopsy in the majority of cases.

An exception occurs when CAA-related inflammation is suspected or when neuroimaging and other investigations are unable to discriminate other potential causes of intracerebral haemorrhage such as an underlying tumour.

Some patients with a large haemorrhage require surgical evacuation due to further neurological deterioration. Previous assumptions that fragile amyloid-laden vessels within the intracerebral haematoma pose a particularly high risk of intra and post-operative bleeding appears to be unfounded.[7]

Table 2: Classic and modified Boston criteria for the diagnosis of cerebral amyloid angiopathy (CAA).[7]

Definite CAA
Full post-mortem histopathological examination demonstrating: - Lobar, cortical or cortical-subcortical haemorrhage   - Severe CAA with vasculopathy   - Absence of other diagnostic lesion
Probable CAA with supporting pathology
Clinical data and pathological tissue (evacuated haematoma or cortical biopsy) demonstrating: - Lobar, cortical or cortical-subcortical haemorrhage   - Some degree of CAA in specimen   - Absence of other diagnostic lesion
Probable CAA
Age ≥55 years   Clinical data and MRI (or CT) demonstrating: - Multiple haemorrhages restricted to lobar, cortical or cortical-subcortical regions (cerebellar haemorrhage allowed) OR   - Single lobar, cortical or cortical-subcortical haemorrhage, and focal or disseminated superficial siderosis   - Absence of other cause of haemorrhage
Possible CAA
Age ≥55 years old   Clinical data and MRI (or CT) demonstrating: - Single lobar, cortical or cortical-subcortical haemorrhage OR   - Focal or disseminated superficial siderosis   - Absence of other cause of haemorrhage

A study by Greenberg et al.[17] investigating the sensitivity and specificity of cortical biopsy for the diagnosis of CAA found that despite the patchy nature of the disease, the complete absence of vascular amyloid in an adequate tissue specimen would largely exclude a diagnosis of CAA.

Q6: How Should we Manage Patients with CAA-Related Intracerebral Haemorrhage?

Acute management with supportive measures to minimise secondary insults is important, as well as intensive blood pressure lowering to reduce haematoma expansion.[4] Surgical intervention needs to be considered if the patient continues to deteriorate.

Secondary preventive strategies aim to reduce the risk of recurrent CAA-related intracerebral haemorrhage:

1) Both anticoagulants and antiplatelet agents increase the risk of recurrent CAA-related haemorrhagic events and should therefore be avoided unless there is a compelling clinical indication to justify the use of these agents.[7]

2) Results from the PROGRESS trial found that blood pressure lowering (by a mean reduction of 9/4 mmHg) has a protective effect against further haemorrhagic events, irrespective of the presence of hypertension.[18]

REFERENCES

1. Van Gijn J et al. Subarachnoid haemorrhage. Lancet. 2007;369(9558):306–18.

2. Kumar S et al. Atraumatic convexal subarachnoid hemorrhage: clinical presentation, imaging patterns, and etiologies. Neurology. 2010;74(11):893–9.

3. Rosand J, Greenberg SM. Cerebral amyloid angiopathy. The Neurologist. 2000;(6):315-25.

4. Charidimou A et al. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. J Neurol Neurosurg Psychiatry. 2012;83(2):124–37.

5. Charidimou A et al. Prevalence and mechanisms of cortical superficial siderosis in cerebral amyloid angiopathy.

Neurology. 2013;81(7):626–32.

6. Linn J et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology. 2010;74(17): 1346–50.

7. Greenberg SM et al. Petechial hemorrhages accompanying lobar hemorrhage: detection by gradient-echo MRI. Neurology. 1996;46(6):1751–4.

8. Cheng A-L et al. Susceptibility-weighted imaging is more reliable than T2*-weighted gradient-recalled echo MRI for detecting microbleeds. Stroke. 2013;44(10):2782–6.

9. Rico M et al. Headache as a crucial symptom in the etiology of convexal subarachnoid hemorrhage. Headache. 2014;54(3):545-50.

10. Spitzer C et al. Non-traumatic cortical subarachnoid haemorrhage: diagnostic work-up and aetiological background. Neuroradiology. 2005;47(7):525–31.

11. Charidimou A et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. Stroke. 2012;43(9):2324–30.

12. Izenberg A et al. Crescendo transient aura attacks a transient ischemic attack mimic caused by focal subarachnoid hemorrhage. Stroke. 2009;40(12):3725–9.

13. Linn J et al. Superficial siderosis is a warning sign for future intracranial hemorrhage. J Neurol. 2013;260:176-181.

14. Wollenweber FA et al. Prevalence of cortical superficial siderosis in patients with cognitive impairment. J Neurol. 2014;261(2):277–82.

15. Zonneveld HI et al. Prevalence of cortical superficial siderosis in a memory clinic population. Neurology. 2014;82(8):698–704.

16. Kinnecom C et al. Course of cerebral amyloid angiopathy–related inflammation. Neurology. 2007;68(17):1411–6.

17. Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid agiopathy. Sensitivity and specificity of cortical biopsy. Stroke. 1997;28(7):1418–22.

18. Arima H et al. Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy the PROGRESS trial. Stroke. 2010;41(2):394–6.

19. Cuvinciuc V et al. Isolated acute nontraumatic cortical subarachnoid hemorrhage. AJNR Am J Neuroradiol. 2010;31(8):1355–62.