Cerebral amyloid angiopathy: a transient ischaemic attack mimic

Authors: Amy Illsley^A and Hawraman Ramadan^B

Cerebral amyloid angiopathy is a commonly occurring condition that is not familiar to most clinicians. A common presenting feature may be transient focal neurological symptoms leading to the potential for clinical misdiagnosis as transient ischaemic attack. This may result in the inappropriate use of anti-platelets and anticoagulants or radiological misdiagnosis. It is also being increasingly recognised as an important cause of spontaneous intracerebral haemorrhage and cognitive impairment in the elderly. Cerebral amyloid angiopathy can be diagnosed based on clinical and radiological findings, but clinicians need a high index of suspicion to ensure appropriate investigations are requested. In this article we aim to cover the pathophysiology, clinical findings, radiological appearances and approach to management of cerebral amyloid angiopathy.

KEYWORDS: Cerebral amyloid angiopathy, convexity subarachnoid haemorrhage, cerebral microbleeds

Introduction

Cerebral amyloid angiopathy (CAA) is being increasingly recognised as an important cause of spontaneous intracerebral haemorrhage (ICH) and cognitive impairment in elderly people. Despite this, it is not a diagnosis familiar to most physicians. The presenting complaint may include transient focal neurological symptoms, leading to misdiagnosis as a transient ischaemic attack (TIA), and subsequent inappropriate anticoagulation or anti-platelet therapy. In this paper the authors aim to cover the basic pathophysiology of CAA, and the clinical findings, radiological appearances and approach to management.

Pathophysiology

Cerebral amyloid angiopathy (CAA) is characterised by progressive deposition of amyloid-β in the wall of small-to medium-sized blood vessels in the cerebral cortex and leptomeninges. It favours posterior cortical regions, followed

Authors: ^ST4 in geriatric medicine, Bradford Royal Infirmary, Bradford, UK; ^Bconsultant neurologist and stroke physician, Bradford Royal Infirmary, Bradford, UK

by frontal temporal and parietal lobes.² CAA can also affect cerebellar vessels, but only rarely those in the brain stem or basal ganglia.² Initially it was thought to be a rarity but recently has been increasingly found to be an important cause of spontaneous ICH, a condition for which very few effective interventions have been identified. A better understanding of CAA may lead to improved clinical management and future therapeutic options.

Amyloid- β is initially deposited in the tunica media, smooth muscle cells and adventitia. As disease progresses, smooth muscle cells are lost, the outer part of the tunica media detaches and fibrinoid necrosis and microaneurysms develop. Microbleeding may then occur and blood breakdown products are deposited around the blood vessels. CAA is also associated with cortical microinfarcts, ischaemic demyelination and gliosis. Based on pathological findings CAA has been split into type 1 and type 2.4 In CAA type 1 the amyloid- β is seen in cortical capillaries, as well as other vessels. In CAA type 2 the amyloid- β is seen in leptomeningeal and cortical arteries, arterioles and veins only. Clinically this is important because CAA type 1 seems to be more closely associated with amyloid deposition in Alzheimer's disease.

A systematic review of four population-based postmortem studies indicated a CAA prevalence of 28–38% in non-demented patients and 55–69% in patients with dementia.⁶ In Alzheimer's disease CAA is found in 82–98% of cases, although severe CAA is seen in only 25% of cases.^{1,7} Advancing age appears to be a risk factor for developing CAA.² In fact, those patients with CAA-related ICH post-mortem were all aged >60 years.¹ Unlike other causes of ICH, CAA has not been found to be associated with traditional cardiovascular risk factors apart from advancing age.² Hypertension is not associated with increased risk of developing CAA but may increase the risk of an ICH.¹

Apolipoprotein E alleles are the only known genetic risk factors for sporadic CAA. Three polymorphisms have been identified in the gene, each causing a single amino acid change, which alters the function of apolipoprotein E.⁸ Some of these alleles have been shown to increase the risk of both CAA and CAA-related ICH.⁸ These alleles and other potentially associated genetic polymorphisms in other genes are an ongoing area of research, and may suggest future therapeutic interventions.¹ There are some very rare inherited forms of CAA, in which onset tends to be earlier and disease manifestations more severe.⁹

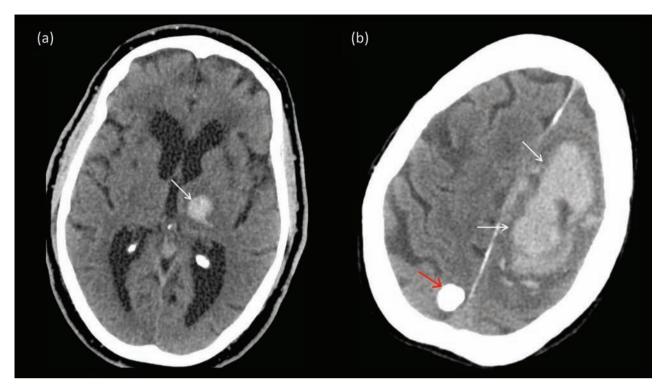


Fig 1. Non-contrast head CT scan of two different patients revealing an acute haemorrhage (white arrow) in (a) the left (deep) thalamus and (b) the left (lobar) frontoparietal lobe, secondary to hypertensive arteriopathy and probable cerebral amyloid angiopathy, respectively. The red arrow shows incidental calcified meningioma. CT = computed tomography.

Clinical features

CAA is most often diagnosed, in life, as a cause of spontaneous ICH in elderly people. CAA-related ICHs are, in contrast to those secondary to hypertension, usually cortical or subcortical (Fig 1), and most commonly in the posterior cortex.² The diagnosis of CAA should also be considered in cases of simultaneous or sequential cortical haemorrhages in patients aged >55 years. Studies suggest that CAA is responsible for 5–10% of spontaneous ICH.² Although initial CAA-related bleeds may be milder than deeper bleeds secondary to hypertension, patients are at risk of recurrent haemorrhage caused by CAA pathology and seizures resulting from the cortical location of bleeds.¹⁰ CAA may also be an important risk factor for ICH related to anticoagulation.¹

Evidence suggests that CAA contributes to cognitive impairment and dementia. The prevalence of CAA is consistently higher in patients with dementia found postmortem, even after controlling for age- and dementia-related neuropathologies. There is also the suggestion that severe CAA may worsen cognitive impairment in Alzheimer's disease. Another rare but important manifestation of CAA is CAA-related inflammation (also known as cerebral amyloid angiitis, amyloid-β-related angiitis and cerebral amyloid inflammatory vasculopathy). CAA-related inflammation generally affects older adults with acute/subacute cognitive decline, headache, behavioural change, seizures and focal neurological deficits. Magnetic resonance imaging (MRI) shows patchy or confluent T2-weighted or fluid-attenuated

inversion recovery (FLAIR) white matter hyperintensities.¹³ On T2*- weighted, gradient-recalled echo (T2*-GRE) or susceptibility-weighted imaging (SWI), inflammation associated with leptomeningeal enhancement and focal oedema, as well as features consistent with CAA, may be seen (see 'Neuroimaging' below) on MRI. Definitive diagnosis requires brain biopsy. A high index of suspicion is needed because it may respond well to immunosuppressive therapy.¹³

Some patients with CAA, similar to the case outlined in Box 1, present with recurrent 'amyloid spells', or transient focal neurological episodes, most commonly spreading paraesthesias.14 Associated neuroimaging findings include cortical microbleeds (CMBs) and convexity subarachnoid haemorrhages (cSAHs) in the cortical regions relevant to the symptoms.¹⁵ This is an important diagnosis because it is easily misdiagnosed as recurrent transient ischaemic attacks, which could lead to use of anti-platelets or other forms of anticoagulation, with potentially catastrophic consequences given the patient's increased risk of ICH from underlying CAA. The stereotypical nature of these attacks, as well as the spreading nature, should alert the clinician to the possibility of a diagnosis of CAA. The episodes respond to antiepileptic drugs, suggesting underlying seizure activity. The aetiology of amyloid spells is not clearly established but a number of potential explanations exist. The haemosiderin deposition after a cSAH is thought to be a cerebral irritant, causing focal seizures. The spreading nature of sensory symptoms has prompted some comparisons to the cortical spreading depression process seen in migraine,

in the case of CAA triggered by microbleeds or inflammation around a blood vessel. Vasospasm secondary to blood products is another explanation. Larger studies are needed to establish the pathophysiology further.¹

Neuroimaging

CAA-related ICH has some distinctive radiological findings that aid diagnosis. The following are features suggestive of underlying CAA:¹

- > convexity SAH
- > location of bleeds typically posterior cortical/subcortical
- > cerebral microbleeds (best seen on MRI T2* or SWI sequences)
- > confluent white matter hyperintensities (leukoaraiosis)
- cortical superficial siderosis (represents chronic lesion after an acute cortical SAH)
- subclinical, small, predominantly cortical infarcts, probably reflecting small vessel occlusion seen in advanced disease
- centrum semiovale-enlarged perivascular spaces (EPVSs) recently suggested as a new marker of CAA.^{16,17}

MRI detects the consequences of CAA but in some trials positron emission tomography, using a radioligand that attaches to amyloid in the brain, has been successfully used in assessing amyloid and this may indicate a future diagnostic tool. ^{1,18} Fig 2 demonstrates some of the radiological features of CAA. Current guidelines in TIA management do not recommend routine blood-sensitive MRI sequences, but the authors suggest that, if a diagnosis of CAA is suspected, the clinician should consider requesting these sequences. ¹⁹

Box 1. Case study.

A 76-year-old, healthy, right-handed man was admitted to the stroke unit with a 1-week history of five brief stereotypical attacks involving numbness of the right hand and right side of the face, associated with dysarthria. On examination, his blood pressure was 145/90 mmHg and neurological and systemic examinations were normal. He was admitted to hospital with a differential diagnosis of multiple transient ischaemic attacks (TIAs). He had a normal full blood count, urea and electrolytes, random plasma glucose, serum cholesterol, thyroid function test, Doppler ultrasonography of the carotid arteries and a 12-lead ECG. A non-contrast cranial CT scan showed convexity subarachnoid haemorrhage (cSAH) over the posterior left parietal lobe (Fig 2a). Magnetic resonance imaging (MRI) of the brain found considerable cortical siderosis with a few cerebral microbleeds (Fig 2b-d). These findings on CT and MRI are consistent with underlying cerebral amyloid angiopathy, resulting in cSAH and haemosiderin deposition on the brain surface. He was successfully treated with lamotrigine for recurrent focal sensory seizures.

cSAH = convexity subarachnoid haemorrhages; CT = computed tomography; ECG = electrocardiography; MRI = magnetic resonance imaging; TIA = transient ischaemic attack.

Diagnostic criteria

The most commonly used diagnostic criteria are the Boston criteria (Box 2).²⁰ The sensitivity of the Boston criteria is improved with T2*-GRE and SWI MRI, so clinicians should consider requesting these sequences or making it clear to the radiologist that they are looking for evidence of CAA, so appropriate MRI sequences are needed.²¹

Management of cerebral amyloid angiopathy

There is no specific treatment for CAA.¹ As with any form of ICH there is evidence that controlling blood pressure is beneficial to reduce haematoma expansion in the acute phase.²² The role of neurosurgery is less clear but trials are ongoing.²³ The STICH II trial recently compared early surgical haematoma evacuation with initial medical management for a small (10–100 ml), supratentorial ,spontaneous ICH with 48 hours of ictus. It found that

early surgery did not increase death or disability at 6 months, and may give a small survival advantage, although this result was not statistically significant (odds ratio [OR] 0.82 [95% confidence interval [CI] 0.62-1.2], p = 0.367). We would advise that current national guidelines for management of ICH

Box 2. Boston criteria for diagnosis of cerebral amyloid angiopathy.

1 Definite CAA

Full post-mortem examination demonstrating:

- > Lobar, cortical or cortical—subcortical haemorrhage
- > Severe CAA with vasculopathy
- > Absence of other diagnostic lesion

2 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

3 Probable CAA

Clinical data and MRI or CT scan demonstrating:

- Multiple haemorrhages restricted to lobar, cortical or corticalsubcortical regions (cerebellar haemorrhage allowed)
- Or single lobar, cortical or cortical—subcortical haemorrhage and focal or disseminated superficial siderosis
- > Age ≥55 years
- > Absence of other cause of haemorrhage

4 Possible CAA

Clinical data and MRI or CT scan demonstrating:

- > Single lobar, cortical or cortical—subcortical haemorrhage
- Or focal (siderosis restricted to three or fewer sulci) or disseminated superficial siderosis (siderosis affecting at least four sulci)
- > Age ≥55 years
- > Absence of other cause of haemorrhage

 $\mbox{CAA} = \mbox{cerebral}$ amyloid angiopathy; $\mbox{CT} = \mbox{computed tomographt; MRI} = \mbox{magnetic resonance imaging.}$

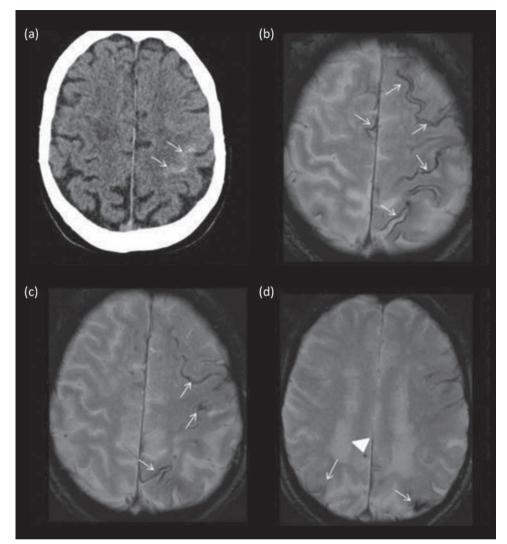


Fig 2. (a) Axial unenhanced CT scan of the brain shows linear hyperdensity (white arrows) in the left central sulcus, indicating acute convexity subarachnoid haemorrhage (cSAH). (b-d) Signal losses on axial gradient echo T2*-weighted MRI sequences over several sulci of both hemispheres (white arrows), indicating disseminated siderosis from previous asymptomatic cSAH and cortical microbleed (arrowhead). cSAH = convexity subarachnoid haemorrhage; CT = computed

tomography; MRI = magnetic resonance imaging.

are followed. The PROGRESS trial looked at a subgroup of 6,105 CAA patients and found that treatment with perindopril, with or without indapamide, reduced the risk of probable CAA-related ICH (as defined by the Boston criteria, Box 2) by 77% (95% CI 19–93%) over a follow-up period of 3.9 years. The numbers were small with a wide confidence interval and further research is needed, but it seems reasonable to suggest that patients with CAA are prescribed antihypertensive medications where appropriate.

Following a diagnosis of CAA or CAA-related ICH the clinician needs to consider the risk of further bleeding. As these patients are often older the risk and benefit of treatments such as anti-platelets and anticoagulation need to be carefully considered. Further studies are needed to evaluate this risk and establish the risk and safety profile of anti-platelets and anticoagulant in CAA. We would suggest, for the moment, that anticoagulants are avoided in patients who have experienced CAA-related ICH and would again stress the importance of diagnosing CAA-related 'amyloid attacks' rather than treating these patients with anti-platelets for presumed recurrent TIAs.

Conclusion

CAA is a commonly occurring condition that is underrecognised by clinicians, leading to the potential for clinical
misdiagnosis as TIAs resulting in inappropriate use of
antiplatelets and anticoagulants or radiological misdiagnosis.
CAA can be diagnosed based on clinical and radiological
findings but clinicians need a high index of suspicion to
ensure appropriate that MRI sequences are ordered. We would
recommend management of hypertension and rationalisation
of anti-platelets and anticoagulants in patients with CAA.
Further research is needed to improve diagnosis and to
establish tailored treatment options to halt progression or
reduce complications, such as ICH.

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Address for correspondence: Dr A Illslay, Bradford Royal Infirmary, Duckworth Lane, Bradford, West Yorkshire BD9 6RJ. Email: aillsley@doctors.org.uk