Cerebral amyloid angiopathy: Review of clinico-radiological features and mimics

Rohit Sharma,1,2 Stephanie Dearaugo,1,2 Bernard Infeld,1,2 Richard O’Sullivan1,3 and Richard P Gerraty1,2

1 Department of Medicine, Monash University, The Alfred Hospital, Melbourne, Victoria, Australia
2 Epworth HealthCare, Richmond, Victoria, Australia
3 Healthcare Imaging Services, Melbourne, Victoria, Australia

R Sharma MBBS(Hons), BMedSc(Hons); S Dearaugo MBBS(Hons), BMedSc(Hons); B Infeld MBBS, PhD, FRACP; R O’Sullivan MBBS, FRANZCR; RP Gerraty MBBS, MD, FRACP.

Correspondence
Dr Rohit Sharma, Department of Medicine, Monash University, The Alfred Hospital, 55 Commercial Rd, Melbourne, Vic. 3004, Australia.
Email: r.sharma@live.com

Conflict of interest: The authors declare that they have no conflict of interest.

Submitted 12 December 2017; accepted 1 March 2018.
doi:10.1111/1754-9485.12726

Summary
Cerebral amyloid angiopathy (CAA) is an important cause of lobar intracerebral haemorrhage (ICH) in the elderly, but has other clinico-radiological manifestations. In the last two decades, certain magnetic resonance imaging (MRI) sequences, namely gradient-recalled echo imaging and the newer and more sensitive susceptibility-weighted imaging, have been utilised to detect susceptibility-sensitive lesions such as cerebral microbleeds and cortical superficial siderosis. These can be utilised sensitively and specifically by the Modified Boston Criteria to make a diagnosis of CAA without the need for ‘gold-standard’ histopathology from biopsy. However, recently, other promising MRI biomarkers of CAA have been described which may further increase precision of radiological diagnosis, namely chronic white matter ischaemia, cerebral microinfarcts and lobar lacunes, cortical atrophy, and increased dilated perivascular spaces in the centrum semiovale. However, the radiological manifestations of CAA, as well as their clinical correlates, may have other aetiologies and mimics. It is important for the radiologist to be aware of these clinico-radiological features and mimics to accurately diagnose CAA. This is increasingly important in a patient demographic that has a high prevalence for use of antiplatelet and antithrombotic medications for other comorbidities which inherently carries an increased risk of ICH in patients with CAA.

Key words: cerebral amyloid angiopathy; intracranial haemorrhage; magnetic resonance imaging; stroke.

Introduction
Cerebral amyloid angiopathy (CAA) was first described by Oppenheim in 1909,1,2 and is characterised by the deposition of beta-amyloid proteins in cortical and leptomeningeal vessels.3 CAA is being increasingly recognised as an important cause of intracerebral haemorrhage (ICH) in the elderly, accounting for up to one-fifth of all spontaneous ICH in this demographic,2 however, CAA has numerous additional clinico-radiological features that are important to recognise for its early diagnosis. This review will provide a brief overview of the pathophysiology of sporadic CAA and will subsequently detail the resultant clinico-radiological manifestations as well as their mimics.

Overview of pathophysiology
The amyloid-β in CAA is predominantly a soluble 40-amino-acid-long form (Aβ1-40, henceforth ‘Aβ’); this is in contrast to the parenchymal amyloid-β in senile plaques of Alzheimer disease (AD) which is predominantly a longer and less soluble 42-amino-acid-long form (Aβ1-42).4 These amyloid proteins are derived from a larger amyloid precursor protein (APP), encoded by the APP gene on chromosome 21.5 APP is produced in many areas of the body, but is expressed and metabolised into Aβ in especially high levels by neurons in the brain.6-8

The leading hypothesis addressing why intravascular Aβ deposition occurs in CAA considers the condition to be a ‘protein elimination failure angiopathy,’9 whereby there
is a defect in the central nervous system (CNS) clearance mechanism of interstitial fluid (ISF), and thus, also the $\text{A}_\beta$ produced by neurons.$^6,10$ ISF drainage is primarily thought to occur via ‘perivascular drainage’, whereby the tunica adventitia of arterioles is continuous with the subarachnoid space and cerebrospinal fluid (CSF) in regions known as ‘perivascular spaces’ (PVS), and that these spaces carry ISF, and hence $\text{A}_\beta$, in a retrograde fashion to the cervical lymphatic system.$^9,11$ Impairment of this pathway can be caused by arteriosclerosis with aging, microinfarction or microtrauma, and can lead to $\text{A}_\beta$ deposition in the outer layers of these vessels.$^4,12,13$

Neuropathologically, in the early stages, $\text{A}_\beta$ deposition is limited to the tunica adventitia resulting in thickening of the vessel.$^{14,15}$ However, with progression, the tunica adventitia becomes saturated resulting in further $\text{A}_\beta$ deposition in the smooth muscle of the tunica media and further thickening of the vessel wall, leading to loss of normal vascular reactivity.$^{16}$ Due to cytotoxic effects of $\text{A}_\beta$, there is subsequent degeneration and eventual loss of the smooth muscle, resulting in thinning and fragility of the vessel wall.$^{14-17}$ During advanced stages, $\text{A}_\beta$ weakens the extracellular matrix resulting in the separation of the tunica intima from the tunica media.$^{14,18,19}$

Cerebral amyloid angiopathy topographically preferentially affects cortical and leptomeningeal vessels, instead of vessels in the cerebellum, brainstem and basal ganglia, in a characteristic patchy manner, whereby foci of advanced CAA may be adjacent to normal unaffected vasculature.$^{15}$ CAA also has a predilection for the posterior brain, especially the occipital lobe,$^{20-24}$ potentially because occipital vessels are inherently thicker and can therefore accommodate more $\text{A}_\beta$ deposition when compared to vessels from other regions of the brain.$^{22}$

Although not associated with other systemic amyloidoses,$^{10}$ sporadic CAA has known genetic risk factors in apolipoprotein E (APOE) alleles, whereby APOE is an important lipoprotein involved in ISF drainage pathways.$^{15}$ The two alleles thought to be implicated in increasing risk of developing sporadic CAA are APOE $\varepsilon2$ and APOE $\varepsilon4$, where APOE $\varepsilon2$ induces vessel fragility, whereas APOE $\varepsilon4$ promotes $\text{A}_\beta$ intravascular deposition.$^{25,26}$ Another common genetic risk factor is Down syndrome or trisomy 21, presumably because there is increased expression of APP, and thus $\text{A}_\beta$, because the APP gene is located on chromosome 21.$^5$ It is thought that additional genetic risk factors are likely to exist and this is a focus of on-going research.$^{15}$ Importantly, CAA is considered to be a distinct, yet highly associated, entity to AD, with up to 90% of those with AD having pathologically determined CAA, but only 25% of patients with advanced CAA having AD.$^{27}$

**Lobar intracerebral haemorrhage**

Spontaneous ICH is the most disabling manifestation of the rupture of thin and fragile $\text{A}_\beta$-laden vessels in CAA, and accounts for up to 74% of all spontaneous ICH in the normotensive elderly population.$^{28,29}$ Due to $\text{A}_\beta$ deposition having a predilection for cortical and leptomeningeal vessels, CAA-related ICH tends to therefore occur in peripheral cortical and subcortical ‘lobar’ locations.$^{29,30}$

The characteristic lobar location of CAA-related ICH is important because it is a key differentiating factor from causes of ICH in ‘deep’ locations, such as chronic hypertensive arteriopathy, which tends to preferentially affect the basal ganglia and pons in a similar elderly demographic.$^{31}$ ICH in the cerebellum may be due to either CAA or chronic hypertensive arteriopathy, and recently it has been described that haemorrhages that are more ‘superficial’ in the cerebellum, such as those restricted to the cerebellar cortex and vermis, are more likely due to CAA compared to those that are ‘deep’ in the cerebellum, such as near the dentate nuclei, which are more likely due to chronic hypertensive arteriopathy.$^{32}$

Clinical manifestations of lobar ICH vary depending on the location and size of the haemorrhage,$^{30}$ but include headache, focal neurological deficits, focal seizures, nausea and vomiting, and depressed conscious state.$^{13,33}$ Radiologically, lobar ICH is commonly initially rapidly evaluated by computed tomography (CT) in the emergency department, where the acute haemorrhage is hyperdense with surrounding hypodense perihaeatomal oedema and evidence of mass-effect (Fig. 1).$^{33}$ Furthermore, the ICH can extend into the overlying convexity subarachnoid space, the lateral ventricles or subdural space.$^{30}$

**Fig. 1.** Acute CAA-related frontal lobar ICH (white arrowhead) on axial CT as a rounded hyperdense lesion with hypodense perihaeatomal oedema.
Cerebral amyloid angiopathy-related lobar ICH tends to be recurrent in nature, with recurrence rates of up to 30% per year having been reported. Having a personal history of ICH recurrence or possession of the APOE ε2 and APOE ε4 alleles have all been shown to independently increase the risk of future CAA-related lobar ICH recurrence. Furthermore, presence of other clinico-radiological features or use of antiplatelet or anticoagulant therapies may also increase the risk of CAA-related ICH and its recurrence.

Other clinico-radiological features of CAA and the Modified Boston Criteria

The diagnosis of CAA before ICH manifests is paramount, especially given the high prevalence of antiplatelet and anticoagulant therapies in elderly patients for other comorbidities that can increase the risk of this consequence. Thus, accurate recognition, by radiologists and referring clinicians, of other clinico-radiological features of CAA that may precede ICH is important. Clinically, patients can also develop transient focal neurological symptoms (TFNS) from convexity subarachnoid haemorrhage (cSAH), or cognitive impairment. However, as approximately 50% of patients with CAA aged over 80 years report no clinical manifestations, the role of the radiologist in recognition of CAA’s radiological features is vital in its early diagnosis.

Magnetic resonance imaging (MRI) sequences that are sensitive to the chronic blood break-down product hemosiderin, namely gradient-recalled echo (GRE) and the newer and more sensitive susceptibility-weighted imaging (SWI), can be used to detect cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS) that are associated with CAA. These are not only markers of CAA, but have also each been shown to be independent risk factors for lobar ICH and its recurrence.

Cerebral microbleeds and cSS have been incorporated into the Modified Boston Criteria (Table 1) which allows for reliable diagnosis of CAA without the need for histopathology. These criteria expand on earlier work by Greenberg et al. who created the original Boston Criteria in 1995, and the diagnosis of ‘probable CAA’ has a sensitivity of 95% and specificity of 81% in a validation study using GRE. This sensitivity and specificity may be even higher if SWI was used instead.

In addition to CMBs and cSS, chronic white matter ischaemia (WMI), cerebral microinfarcts and lobar lacunes, cortical atrophy, and increased dilated perivascular spaces in the centrum semiovale (CSO-DPVS) have each been recently described as promising MRI biomarkers of CAA that may have potential to become additions to future diagnostic criteria. Furthermore, an autoimmune response to Aβ, ‘CAA-related inflammation’ (CAA-rI), is another manifestation of CAA that is important to recognise.

Table 1. Modified Boston Criteria for diagnosis of CAA

<table>
<thead>
<tr>
<th>Classification</th>
<th>Modified Boston Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite CAA</td>
<td>Full post-mortem examination demonstrating:</td>
</tr>
<tr>
<td></td>
<td>- Lobar, cortical, or corticosubcortical haemorrhage</td>
</tr>
<tr>
<td></td>
<td>- Severe CAA with vasculopathy</td>
</tr>
<tr>
<td></td>
<td>- Absence of other diagnostic lesion</td>
</tr>
<tr>
<td>Probable CAA with supporting pathology</td>
<td>Clinical data and pathological tissue (evacuated haematoma or cortical biopsy) demonstrating:</td>
</tr>
<tr>
<td></td>
<td>- Lobar, cortical or corticosubcortical haemorrhage</td>
</tr>
<tr>
<td></td>
<td>- Some degree of CAA in specimen</td>
</tr>
<tr>
<td></td>
<td>- Absence of other diagnostic lesion</td>
</tr>
<tr>
<td>Probable CAA</td>
<td>Clinical data and MRI or CT demonstrating:</td>
</tr>
<tr>
<td></td>
<td>- Multiple haemorrhages restricted to lobar, cortical or corticosubcortical regions (cerebellar haemorrhage allowed)</td>
</tr>
<tr>
<td></td>
<td>- Single lobar, cortical or corticosubcortical haemorrhage and focal or disseminated cSS</td>
</tr>
<tr>
<td></td>
<td>- Age ≥ 55 years</td>
</tr>
<tr>
<td></td>
<td>- Absence of other cause of haemorrhage or cSS</td>
</tr>
<tr>
<td>Possible CAA</td>
<td>Clinical data and MRI or CT demonstrating:</td>
</tr>
<tr>
<td></td>
<td>- Single lobar, cortical or corticosubcortical haemorrhage</td>
</tr>
<tr>
<td></td>
<td>- Focal or disseminated cSS</td>
</tr>
<tr>
<td></td>
<td>- Age ≥ 55 years</td>
</tr>
<tr>
<td></td>
<td>- Absence of other cause of haemorrhage or cSS</td>
</tr>
</tbody>
</table>

Cerebral microbleeds

Cerebral microbleeds, or ‘microhaemorrhages’, refer to small 2–10 millimetre, round or ovoid, low-signal areas that are evident on susceptibility-sensitive MRI (Fig. 2). Histologically, they represent small areas of blood extravasation into the PVS. Similar to CAA-related ICH, CMBs in CAA also have a lobar distribution, while those associated with chronic hypertensive arteriopathy tend to instead be located in deep regions of the brain. In addition to CAA and chronic hypertensive arteriopathy, there are numerous other aetiologies of CMBs (Table 2) as well as many radiological mimics (Table 3) to be aware of.

Interestingly, the sizes of haemorrhages in CAA fit a bimodal distribution, with the implication being that there are two distinct sizes for haemorrhages in CAA: CMBs (‘microhaemorrhages’) and lobar ICH (‘macrohaemorrhage’). Reasons for this bimodal distribution may be revealed by a theory proposed by Miller Fisher in 1971. He proposed that a vessel could rupture and then either disrupt adjacent vessels through shear forces resulting in ‘avalanche-like’ expansion of the bleed into an ICH, or not cause these shear forces and remain a CMB. A recent study utilising computer-based simulation techniques supports this theory by also demonstrating this bimodal distribution.

Although lobar CMBs were initially thought to be asymptomatic lesions, there is growing evidence that they are a contributor to cognitive decline, with an...
analysis of The Rotterdam Scan Study showing that the presence of numerous lobar CMBs was independently associated with decreased cognitive function, and in particular, executive function. However, this is only thought to be one factor contributing to cognitive impairment in CAA, as discussed later in this review.

### Convexity subarachnoid haemorrhage, cortical superficial siderosis, and transient focal neurological symptoms

Convexity subarachnoid haemorrhage (cSAH) is a non-aneurysmal SAH, characterised by bleeding localised to one or more adjacent cortical sulci at the convexity of the brain, without spread to the basal cisterns, the Sylvian fissure, the interhemispheric fissure or the ventricles. This particular spatial localisation differentiates it from aneurysmal or perimesencephalic SAH, which tend to have predilections for those other areas. Although cSAH can uncommonly result from a primary lobar ICH that simply extends secondarily into the subarachnoid space as it grows, pathological and radiological studies have found that the vast majority of cSAH in CAA

---

**Table 2. Causes of CMBs other than CAA and chronic hypertensive arteriopathy**

<table>
<thead>
<tr>
<th>Cause of CMB</th>
<th>Brief description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse axonal injury</td>
<td>Traumatic brain injury causing shearing of axons and adjacent capillaries resulting in numerous CMBs.</td>
</tr>
<tr>
<td>Cerebral vasculitis</td>
<td>Inflammation of blood vessels in the CNS can compromise affected blood vessels leading to CMBs.</td>
</tr>
<tr>
<td>Cerebral cavernous malformations</td>
<td>Vascular malformations that can be multiple and part of familial syndromes such as multiple cavernoma syndrome. zabramski Classification type IV cavernous malformations are CMBs described as ‘punctate hypointense foci’ on GRE.</td>
</tr>
<tr>
<td>Haemorrhagic metastases</td>
<td>Some cerebral metastases, such as melanoma or renal cell carcinoma, can be haemorrhagic and can produce CMBs.</td>
</tr>
<tr>
<td>Infection (e.g. infective endocarditis, malaria)</td>
<td>Rupture of cerebral mycotic aneurysms can result in CMBs, whereas cerebral septic embolisation can also result in petechial CMBs.</td>
</tr>
<tr>
<td>Cerebral fat embolism</td>
<td>Sequela of long bone trauma or orthopaedic surgery resulting in CMBs in a ‘starry sky’ pattern from fat embolisation.</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Potentially due to hypoxia-induced hydrostatic or chemical effects on the blood-brain barrier resulting in CMBs.</td>
</tr>
<tr>
<td>Hypoxaemia (e.g. acute respiratory distress syndrome, high-altitude exposure)</td>
<td>Rupture of small collateral vessels, especially in patients of Asian descent.</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>Rare autosomal dominant condition with an underlying defect affecting smooth muscle cells of small cerebral blood vessels. Although ischaemia is predominant, CMBs can occur in up to 69% of patients.</td>
</tr>
<tr>
<td>Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy</td>
<td>A condition with an unclear aetiology, but often associated with hypertension or immunosuppressive therapy, that is radiologically characterised by symmetrical white matter vasogenic oedema in the posterior cerebral hemispheres; CMBs are known to occur in up to 65% of patients.</td>
</tr>
<tr>
<td>Posterior reversible encephalopathy syndrome (PRES)</td>
<td>Rare autosomal dominant condition with an underlying defect affecting type IV collagen, associated with subcortical CMBs in up to 53% of patients, as well as ischaemia.</td>
</tr>
<tr>
<td>COL4A1 small-vessel arteriopathy</td>
<td>Fulminant variant of acute disseminated encephalomyelitis characterised by gross cerebral oedema, tumefactive lesions and development of CMBs.</td>
</tr>
<tr>
<td>Acute haemorrhagic leukoencephalitis (Weston–Hurst syndrome)</td>
<td>Spectrum of disorders characterised by microvascular occlusions resulting in focal regions of infarction and CMBs.</td>
</tr>
<tr>
<td>Thrombotic microangiopathies</td>
<td>Rare lymphoma characterised by intravascular tumour cell proliferation leading to focal regions of infarction and CMBs.</td>
</tr>
<tr>
<td>Intravascular lymphoma</td>
<td>Rare neurovascular disorder where CMBs can manifest in the brain ipsilateral to the facial hemiatrophy,</td>
</tr>
<tr>
<td>Progressive facial hemiatrophy (Parry–Romberg syndrome)</td>
<td></td>
</tr>
</tbody>
</table>
actually occurs due to rupture of fragile Aβ-laden convexity leptomeningeal vessels.42,44,78,79

Although cSAH can present with the ‘thunderclap headache’ that is classically associated with SAH, the headache in cSAH tends to either be very mild or does not occur at all.76 Instead, the presentation may be with transient focal neurological symptoms (TFNS) or ‘amyloid spells’.76 TFNS are characteristically described as recurrent, stereotyped, spreading paraesthesias lasting several minutes,80,81 but a range of both positive (e.g. visual symptoms) and negative (e.g. paresis, dysphagia) transient symptoms have been described.82 TFNS, especially manifesting with spreading paraesthesias, are more likely to occur when the cSAH is localised to the central sulcus, which is in close proximity to the primary motor and sensory cortices.83,84 The precise pathophysiology of TFNS is uncertain; however, the leading hypothesis considers cortical spreading depression as the primary mechanism, whereby products released during the breakdown of cSAH blood induce a spreading wave of depolarisation in the adjacent cortex.82,85

It is imperative to make a distinction between TFNS and sensory transient ischaemic attacks, which may be instead included in the referral note, but will tend to only have negative symptoms without migration.81 This distinction is important to be aware of because misdiagnosis and subsequent initiation or escalation of antiplatelet and anticoagulant therapy in these patients who actually have CAA unnecessarily increases their risk of lobar ICH.86 Other clinical mimics of TFNS that a referring clinician may be querying include migrainous aura, where symptoms may also evolve over a period of minutes in a usually younger demographic,86 and focal Jacksonian epileptic seizures, where symptoms evolve over a period of seconds.30

Radiologically and acutely, cSAH can be detected by both CT and MRI. On CT, cSAH may appear as a subtle curvilinear hyperdensity localised to one or more adjacent sulci.87 However, T2 FLAIR MRI sequences are more sensitive, where the haemorrhage will actually appear as high signal.87,88 Sub-acute and chronically, susceptibility-sensitive MRI sequences can be used to detect the low-signal hemosiderin residues that are left after cSAH resolution, known as cortical superficial siderosis (cSS) (Fig. 3).44

Notably, a retrospective study analysing MRI data from patients who presented with acute cSAH, in the form of TFNS in 80% of cases, found that over 90% of the

<table>
<thead>
<tr>
<th>CMB mimic</th>
<th>Differentiating characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow voids of cortical veins</td>
<td>Curvilinear lesions in subarachnoid space that may traverse through multiple axial slices and drain into flow voids of other vessels, also often visible on T2.39,68</td>
</tr>
<tr>
<td>Calcification (e.g. neurocysticercosis)</td>
<td>Hyperdense on CT although SWI filtered phase imaging may also be useful.39,68–70</td>
</tr>
<tr>
<td>Cerebral cavernous malformations</td>
<td>Usually larger, except Zabramski classification Type IV lesions, that are visible on T1 and T2 and may have a characteristic hemosiderin rim.39,55</td>
</tr>
<tr>
<td>Air (e.g. air–bone interfaces, postoperative pneumocephalus)</td>
<td>Obvious from location (e.g. air–bone interfaces) or clinical history of recent neurosurgery or trauma.39,68,71</td>
</tr>
<tr>
<td>Metal (e.g. metallic emboli)</td>
<td>Hyperdense on CT and should have clues on clinical history.71</td>
</tr>
</tbody>
</table>

Fig. 3. Appearance of cSAH (white arrowheads) of the same patient on (a) axial CT showing a curvilinear hyperdensity and (b) axial T2 FLAIR MRI also showing a curvilinear region of high signal, and early appearance of cSS on (c) axial SWI MRI as a curvilinear region of low signal (note that other sulci remote to the acute bleed are already affected by cSS).
patients already had evidence of cSS, despite not necessarily having had previous presentations of cSAH. Hence, it is thought that detection of cSS by the radiologist can be utilised as proof of not only symptomatic cSAH, but also prior silent cSAH. Although CAA is likely the most common cause of cSS and cSAH in those aged 65 years or more, there are other aetiologies to consider (Table 4). Furthermore, it is important to not confuse cSS with the similarly named 'superficial siderosis of the CNS', which is a rare condition unrelated to CAA and of unknown aetiology, characterised by infratentorial superficial siderosis resulting in sensorineural deafness, cerebellar ataxia and pyramidal signs. Additionally, cSS also has a number of radiological mimics (Table 5).

**White matter ischaemia, cerebral microinfarcts and lobar lacunes, and cortical atrophy**

Not only can CAA result in haemorrhage, but it is also thought to be implicated in ischaemia and infarction. White matter (WM) primarily consists of myelinated axons that connect different areas of grey matter, such as the cortex and basal ganglia. In the cerebral hemispheres, the WM receives its blood supply exclusively from small penetrating arterioles that arise from leptomeningeal arteries and then traverse through the cortex before supplying the underlying WM. These penetrating arterioles are end arteries and tend not to Anastomose with each other distally. WM, is particularly vulnerable to ischaemia if there is disease, such as CAA, of these penetrating vessels. The loss of vascular smooth muscle in moderate-severe stages of CAA results in impairment of normal cerebrovascular autoregulation mechanisms, and thus these vessels do not react normally to stimuli such as focal hypoxia. This results in not only chronic ischaemia to their supplied WM, but also episodic instances of cerebral microinfarction and development of WM ‘lobar lacunes’.

**Table 4. Other causes of spontaneous supratentorial cSAH and cSS**

<table>
<thead>
<tr>
<th>Cause of cSAH and cSS</th>
<th>Brief description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible cerebral vasostenorrhaphy syndrome (RCVS)</td>
<td>A condition that is more prevalent in a younger demographic, RCVS is characterised by an acute severe inflammation of leptomeningeal blood vessels in the CNS can compromise affected blood vessels leading to haemorrhage.</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>Thrombosis of cerebral veins can cause cSAH through unknown mechanisms, possibly due to haemorrhage of a ‘venous infarct’.</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>Rupture of peripheral leptomeningeal mycotic aneurysms can result in cSAH.</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>Tends to present in a younger demographic and an angiogram will show collateral fillings.</td>
</tr>
<tr>
<td>PRES</td>
<td>cSAH is known to occur in up to 17% of patients.</td>
</tr>
<tr>
<td>Dural ectasia (e.g. due to neurofibromatosis type 1)</td>
<td>Friable vessels at the site of ectatic dura may rupture and bleed into the subarachnoid space; there is likely to be superficial siderosis infratentorially too.</td>
</tr>
</tbody>
</table>

**Table 5. Supratentorial cSS mimics on GRE and SWI MRI**

<table>
<thead>
<tr>
<th>cSS mimic</th>
<th>Differentiating characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow voids of cortical veins</td>
<td>Will not consistently run parallel to the sulci, and can be followed to drain into other vessels.</td>
</tr>
<tr>
<td>Calcification (e.g. Sturge–Weber syndrome)</td>
<td>Visible as hyperintense on CT although phase contrast SWI images may also be useful.</td>
</tr>
<tr>
<td>Haemorrhages within area of infarction</td>
<td>Usually associated with deeper parenchymal damage deep to the cortex.</td>
</tr>
<tr>
<td>Clusters of CMBs</td>
<td>Will appear irregular, rather than smooth and curvilinear.</td>
</tr>
<tr>
<td>Thrombosed cortical vessel</td>
<td>Thrombus may have susceptibility artefact but will not consistently run parallel to the sulci.</td>
</tr>
</tbody>
</table>

© 2018 The Royal Australian and New Zealand College of Radiologists
cortical atrophy, having only been recently described in the literature, requires specialised three-dimensional cortical surface reconstructions to properly appreciate, and thus, is not yet a clinically viable biomarker for CAA.48

Chronic WMI has been found to be an independent risk factor for lobar ICH and increased CMB burden,104 which is unsurprising given that the favoured theory regarding WMI in CAA is that it is related to moderate-severe stage CAA. Furthermore, there is increasing evidence that chronic WMI and cerebral microinfarcts are also contributors, along with CMBs, to cognitive impairment that is independent of AD.105,106 It is not yet clear what contribution, if any, cortical atrophy makes to cognitive decline or other clinical features of CAA.

**Cognitive impairment**

Cerebral microbleeds, chronic WMI, cerebral microinfarcts and lobar lacunes are all thought to be independent contributors to cognitive and functional decline independent of AD in patients with CAA.30 It has been postulated that these lesions cause gradual cognitive impairment by either disrupting neuronal circuits or occurring in strategic locations that could alter cognition.107 This hypothesis was recently tested by comparing reconstructed structural brain networks in non-demented patients with probable CAA and aged control participants, where it was found that there was lower global efficiency of the networks in the group with probable CAA, and that this correlated with increased
number of CMBs and increased volume of WM ischaemia and infarction. Moreover, upon cognitive testing, this study demonstrated that lower global efficiency was also associated with worse performance on tests regarding executive function, a finding that is consistent with that of the large Rotterdam Scan Study. In addition to gradual chronic cognitive decline, patients with CAA can also experience acute stepwise decline in cognitive function after lobar ICH, or may present with a rapidly progressing cognitive decline caused by CAA-ri, which will be discussed later in this review. Furthermore, not only can CAA independently lead to impaired cognition, it can also lower the threshold for clinically overt dementia in patients with AD. It has been shown in numerous studies, including the Honolulu-Asia Aging Study, that patients with both CAA and AD tend to either have more severe cognitive impairment, or require less AD pathology to produce the same amount of cognitive impairment, when compared to someone with AD without CAA.

Centrum semiovale dilated perivascular spaces

Cerebral WM, or ‘centrum semiovale’, dilated perivascular spaces (CSO-DPVS) have recently been described as another potential manifestation of CAA. PVS are the major route for the drainage of ISF, including Aβ, from the brain. It has been proposed that as vessel walls become saturated with Aβ, potentially due to prior damage to the perivascular drainage, this results in retrograde dilation of these PVS, and actually causes further impairment to perivascular drainage. This impaired drainage leads to further Aβ deposition, resulting in a
'vicious cycle'. Indeed, a higher number of MRI-visible CSO-DPVS has been found to correlate with a higher histopathological severity of CAA, and also correlates with the increased presence of CMBS and cSS. In comparison, MRI-visible dilated PVS in the basal ganglia are highly associated with chronic hypertensive arteriopathy instead.

The CSO-DPVS are not appreciable with CT, but on T2 MRI can be seen in the cerebral white matter as either small round or ovoid high-signal regions when imaged perpendicular to the course of their draining vessel, or as thin linear high-signal structures when imaged parallel to the course of their draining vessel (Fig. 6). It is uncertain whether CSO-DPVS contribute to any of the aforementioned clinical features observed in CAA or if their presence indicates a higher risk of lobar ICH and its recurrence.

Cerebral amyloid angiopathy-related inflammation

Cerebral amyloid angiopathy-related inflammation (CAA-ri) is an uncommon autoimmune response to vascular Aβ. Histopathologically, it represents a spectrum of disease, ranging from perivascular inflammation consisting of lymphocytes, macrophages and multinucleated giant cells, to an inflammatory process consisting of granuloma formation and inflammation confined to the Ajladen vessel wall itself. It has not been fully elucidated how these inflammatory processes begin, but it has been postulated that in some individuals with CAA, potentially linked to the APOE ε4 allele, Aβ deposition triggers inflammatory cascades and leads to this presentation.

Clinically, CAA-ri can present with subacute or rapidly progressive cognitive decline, headache, hallucinations, focal neurological signs, focal seizures or decreased consciousness. On CT, CAA-ri manifests as asymmetric hypodense subcortical lesions, while on T2 FLAIR MRI, these lesions have high signal and involve the subcortical U fibres, as appreciable in Figure 7. However, the clinico-radiological features of CAA-ri are common to many different CNS vasculitides and other conditions such as PRES. Hence, to diagnose CAA-ri in the absence of biopsy, susceptibility-sensitive MRI has a role to detect radiological evidence for underlying CAA, such as lobar ICH, CMBS, cSS, and potentially CSO-DPVS, and WM ischaemia and infarcts, which could then strengthen the likelihood of CAA-ri being the diagnosis. This is reflected in a recently proposed diagnostic criteria.

Conclusion

Sporadic CAA is common in the elderly and has many clinico-radiological features that can now be detected before the manifestation of lobar ICH. While only two decades ago, histopathology and CT were the only tools available for its diagnosis, the relatively recent advent of susceptibility-sensitive MRI has revolutionised the diagnosis of this condition and highlighted the key role that radiologists play. However, it is important for radiologists to be aware of the large variety of clinical manifestations that may be included in a referral note, the many mimics and other aetiologies of CMBS and cSS that are part of the Modified Boston Criteria, as well as the other more recently described radiological associations, to accurately diagnose CAA and to contribute to safely managing a demographic that has a high prevalence of use of medications that can increase their risk of ICH.

Acknowledgements

No other persons or organisations have made substantial contributions to this manuscript. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References


48. Greenberg SM, Goldstein JN, Rosand J, Greenberg SM. Modeling intracerebral hemorrhage