Cerebral Amyloid Angiopathy and Intracerebral Haemorrhage

Abstract
Cerebral amyloid angiopathy (CAA) is increasingly recognised, particularly as a cause of intracerebral haemorrhage and dementia. CAA may present to the clinical neurologist in a range of circumstances, including inpatient or outpatient general neurology (with the subacute encephalopathy of CAA-related inflammation, or transient focal neurological episodes), dementia clinics (in particular in association with Alzheimer’s disease) and, of course, in the context of acute stroke (intracerebral haemorrhage). This clinical review article presents an overview of the key clinical, neuropathological and imaging findings in CAA, as well as a practical review of the challenging management aspects relevant to CAA-related intracerebral haemorrhage.

Introduction
Our concept of cerebral amyloid angiopathy (CAA) has radically evolved over time: considered a rare pathological curiosity in the early 20th century, CAA is now an increasingly recognised cause of cerebral haemorrhage and dementia, with important diagnostic and mechanistic implications.¹ This development in our understanding was greatly facilitated by an improved ability to diagnose CAA in vivo, thanks to significant advances in neuroimaging.²⁻⁴ CAA usually presents to clinicians in one of four ways: lobar intracerebral haemorrhage (ICH); dementia or cognitive decline; transient focal neurological episodes; and the encephalopathy seen in acute CAA-related inflammation (Table 1).⁵ The neuropathological coexistence of CAA and Alzheimer’s disease (AD) is well recognised⁶ with pathological evidence of CAA in 80 – 98% of AD brains, but these processes can also occur independently of one another: only 50% of those with CAA meet the pathological criteria for AD, and moderate-to-severe CAA is seen in only 25% of those with AD.⁷ There is also a growing appreciation that the amyloid related imaging abnormalities (ARIA) seen in those with AD receiving amyloid beta (Aβ) immunotherapy bears a striking resemblance to inflammatory CAA, and that the extent of the response may be related to pre-treatment CAA severity, suggesting a role beyond that of innocent bystander in AD pathophysiology.⁸⁻¹¹ The fact that non-Aβ amyloid proteins can also form comparable vascular deposits with similar clinical manifestations¹² has led to a hypothesis that these conditions are all due to failures of normal perivascular protein elimination pathways,¹² which may have therapeutic relevance in the future.

The first half of this short summary aims to introduce CAA by describing its characteristic neuropathological and imaging findings. The second half will explore the role of CAA in ICH, in particular our current diagnostic criteria and the potential management implications CAA has in the context of ICH.

What is Cerebral Amyloid Angiopathy?

Neuropathology
CAA is one of the cerebral small vessel diseases, a broad term that describes any vascular pathology affecting the small (usually <2mm) arteries, capillaries and venules of the brain.¹²⁻¹⁵ CAA particularly affects the cortical and leptomeningeal vessels of the cerebrum and cerebellum, frequently sparing deeper structures such as the basal ganglia, thalamus and brainstem.¹² This progressive vascular deposition of amyloid protein has been described for eight types of amyloid protein, most of which have been identified because they cause inherited forms of CAA that tend to present with dementia or ICH.¹⁴⁻¹¹ As the CAA secondary to Aβ is by far the most common,¹¹ the remainder of this article will focus upon this subtype; subsequent references to CAA are to Aβ CAA.

Aβ protein is formed from the Amyloid Precursor Protein (APP), with the 42 amino acid fragment found mainly in the parenchymal amyloid deposits characteristic of Alzheimer’s disease, and the 40 amino acid form tending to be deposited in the vasculature.¹ Progression and high accumulation of peryvascular Aβ results in smooth muscle loss and eventual “double barrelling” (Figure 1).¹ CAA can be subdivided based upon which type of vessel is affected, with type 1 CAA affecting capillaries as well as arteries and venules, and type 2 being “capillary-sparing”, whilst affecting all other vessel types.¹⁻³ Interestingly, these subtypes appear to be associated with specific alleles of Apolipoprotein E (ApoE) and may have discrete clinical manifestations.² ApoE4 seems to be associated with type 2 CAA,¹ and is also seen more frequently in those with CAA and ICH, as well as those with disseminated cortical superficial siderosis (a haemorrhagic imaging marker of CAA). ApoE4, on the other hand, has been described as “the most prevalent genetic risk factor for sporadic AD”¹⁷ and is also associated with the cognitive decline observed in Alzheimer’s disease.⁸⁻¹¹
Figure 1: Neuropathological changes observed in CAA: the Vonsattel grading scheme for CAA severity.

In mild (grade 1) CAA, Aβ deposits are present in a proportion of the vessel wall. In moderately severe (grade 2) CAA Aβ is deposited circumferentially in the media. In severe (grade 3) CAA, in addition to concentric Aβ deposition, there is splitting and double-barrelling of the vessel wall. Very severe (grade 4) CAA is associated with marked obliteration of the lumen often associated with vascular necrosis, recanalisation and scarring.

Figure and legend courtesy of Zane Jaunmuktane, Division of Neuropathology, UCL Institute of Neurology.

Table 1: The four characteristic clinical presentations of CAA

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Clinical Features</th>
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<tr>
<td>Lobar intracerebral haemorrhage (ICH)</td>
<td>Acute stroke syndrome – may range from mild or asymptomatic to life-threatening.</td>
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<tr>
<td>Dementia or cognitive decline</td>
<td>Processing speed and executive function appear to be particularly affected; note also overlap with Alzheimer’s disease.</td>
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| Transient focal neurological episodes (TFNE; previously termed “amyloid spells”)
  [5, 12]                                         | Recurrent, stereotyped, spreading symptoms (usually paraesthesia, numbness or weakness); spreading over seconds to minutes with resolution over a similar timeframe. |
| CAA-related inflammation
  [13, 14]                                        | Subacute cognitive decline and/or seizures. Imaging typically shows asymmetrical confluent white matter abnormalities; microbleeds may be seen acutely or subacutely. |
|                                                  | There is some evidence that anti-Aβ autoantibodies in the CSF may correlate with disease activity. |
|                                                  | Management is with immunosuppressive therapy (although some patients recover spontaneously). Recurrence is rare but has been described. |

Table 2: Usefull diagnostic MRI markers in CAA

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<tr>
<th>Marker</th>
<th>MRI sequence</th>
<th>Description</th>
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| Strictly Lobar Cerebral Microbleeds (MBs)
  Adapted from references [57-59]                                      | Paramagnetic sequences
e.g. T2*-GRE, SWI | “Haemorrhagic” marker of CAA, thought to represent small self-limiting parenchymal haemorrhages. Black (hypointense) round or ovoid lesions (maximum diameter 10mm), with associated “blooming effect”. Lobar location (rating scales include MARS and BOMBS). |
| Cortical Superficial Siderosis (cSS)                                 | Paramagnetic sequences
e.g. T2*-GRE, SWI | “Haemorrhagic” marker of CAA, believed to be the result of evolution of previous convexity subarachnoid haemorrhage. Dark (hypointense) bilinear ‘track-like’ rim around convexitites of the cerebral hemisphere; restricted to supratentorial compartment in CAA. |
| Enlarged Perivascular Spaces (or Virchow–Robin Spaces) in the Centrum Semiovale (CSO-PVS)
  Adapted from references [60, 61]                                      | T2           | “Non-haemorrhagic” marker of CAA, demonstrating enlargement of the interstitial fluid channels that surround small arterioles. Small white (hyperintense/high signal) round or linear lesions (CSF isointense). |

in normal ageing. It seems to be associated with type 1 CAA pathologically, and CAA without ICH clinically. Mechanistically, this raises the possibility that the size of the affected vessel dictates clinical presentation, with capillary level disease tending to result in cognitive impairment and arteriolar level involvement resulting in ICH; further work is necessary in order to establish whether or not this is the case.

Imaging Markers

The recent advances in our understanding of CAA have been made possible by the identification of new neuroimaging tests that allow a diagnosis to be made without pathological material. Although a number of novel imaging techniques, including diffusion tensor imaging, visual functional MRI and amyloid-PET, have diagnostic potential in CAA, these are not always widely available in clinical practice. Table 2 describes imaging markers of CAA that may be easily identified on standard clinical MR sequences, examples of which are shown in Figure 2.

CAA is diagnosed using either the Classical or Modified Boston Criteria (Table 3). Given the increasing evidence for a “non-haemorrhagic” CAA phenotype, these criteria may require amendments so that those who may be “cognitive-predominant” (i.e. without
macro- or microhaemorrhage) can still be accurately diagnosed.

CAA and ICH – what do we know, and what can be done?

The association between CAA and ICH, in particular lobar ICH, has been recognised for some time; a recent meta-analysis found a significant association between CAA and lobar ICH (OR 2.21, 95% CI 1.09 to 4.45).\(^{18}\) The fact that CAA is associated with lobar ICH in particular has significance, as lobar ICH appear to be more likely to recur, with an annual recurrence rate of between 2.5 – 14.3% compared with 1.3 – 2.9% for non-lobar ICH.\(^{19}\)

Given that the estimated one year survival rate in those with ICH is 46%,\(^ {19}\) and CAA may be responsible for up to 50% of lobar ICH,\(^ {20}\) modifying this risk could have a dramatic effect on ICH rates.

The risk factors for CAA-related ICH can be considered as modifiable or non-modifiable. Non-modifiable risk factors include increasing age, Alzheimer’s disease, and any predisposing genetic factors (for example, inherited forms of CAA, or particular ApoE variants).\(^ {1,21}\) The presence of CAA itself, perhaps the most obvious risk factor for CAA-related haemorrhage, has always been thought of as non-modifiable; the hope is that, with the development of new therapeutic strategies for CAA such as the anti Aβ monoclonal antibody ponezumab,\(^ {22}\) this will change.

The modifiable risk factors for CAA-related ICH are hypertension and the use of drugs that increase overall bleeding risk, for example antiplatelet agents, anticoagulants and thrombolytic strategies.\(^ {1}\) Statin use may also be a modifiable risk factor in this situation. These factors will now be considered in turn.

The main evidence for blood pressure (BP) lowering in CAA comes from a sub-analysis of the PROGRESS trial.\(^ {23}\) This study demonstrated that, even though those with CAA-related ICH tended to have lower BP than those with hypertension-related ICH (137/81mmHg vs 157/88mmHg respectively), it was the CAA group that seemed to benefit the most from BP reduction, with a 77% reduction in CAA-related ICH.\(^ {23}\)

Although PROGRESS did not have a target BP, the trials demonstrated reductions in stroke risk for both hypertensive (>160/90mmHg at baseline) and non-hypertensive groups; the latter group had a mean entry BP of 136/79mmHg and the average BP reduction in the treatment group was 9/4mmHg.\(^ {24}\) Based on this, it seems reasonable to aim for a BP target of ~125/75mmHg, which is also in keeping with the results from SPS3, which showed a significant reduction in ICH in those with a BP less than 130/80mmHg.\(^ {25}\) However, further randomised data in ICH survivors with an aggressive BP treatment target are needed to confirm safety and efficacy in this ICH population. A trial of telemetry-guided intensive BP control is in set up in the UK to address this (Prevention Of Hypertensive Injury to the Brain by Intensive Treatment-ICH – PROHIBIT-ICH, D Werring, personal communication).

As those with CAA are at increased risk of ICH, medications that impair normal haemostasis (antiplatelet drugs, anticoagulants, intravenous thrombolysis) are best avoided, although this is not always possible and presents a difficult clinical dilemma,\(^ {26}\) especially as patients with CAA also appear to be at increased risk of ischaemic events.\(^ {27}\) There is observational evidence in favour of avoiding anticoagulation with warfarin in CAA,\(^ {28,29}\) and there are case reports of ICH in CAA following treatment with intravenous thrombolysis.\(^ {30-32}\) Presence of the ApoE ε2 allele seems to particularly be associated with warfarin related ICH.\(^ {30,32,33}\) However, there are no randomised trial data to inform the use of warfarin in CAA. The role of non-vitamin K

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Figure 2: Commonly encountered MRI markers in CAA. Examples of lobar MBs (A, B), cSS (C, D), and CSO-PVS (E,F).
oral anticoagulants (with about half of the ICH risk of warfarin) in those with CAA and an indication for anticoagulation (e.g. atrial fibrillation) remains to be defined, but our practice at present is to avoid long term oral anticoagulants in CAA unless there is a clear unavoidable need to give them (e.g. metallic heart valves, life-threatening venous thromboembolism). For patients with atrial fibrillation, left atrial appendage occlusion (LAOO) may have a role in patients with CAA as it has similar efficacy to oral anticoagulation with warfarin, but without the need for long term anticoagulation exposure. The case for antplatelet agents as a clear risk factor for future ICH in CAA is less clear cut – aspirin has been the most widely studied, and has been suggested as both increasing the risk of ICH in CAA and a history of recurrent ICH. Further studies are required, but meanwhile care must be taken in how CAA is diagnosed; in particular, with regard to the use of cerebral microbleeds in diagnostic criteria, as these may be a consequence of antiplatelet or anticoagulant treatments in those with and without CAA.

Whether statins increase the risk of future ICH in those with CAA remains uncertain. There is, however, some evidence that they are associated with an increase in microbleed frequency, but whether they increase the risk of ICH remains unclear. There is evidence that lipid lowering can increase ICH risk although there is observational evidence of an association between intracranial haemorrhage (macro- and micro-) with reduced LDL-cholesterol, convincing randomised evidence that lipid lowering can increase ICH risk remains scarce. A decision analysis suggested that in CAA-related ICH the risks of statins for future ICH might outweigh the benefit for prevention of vaso-occlusive disease, but that statins may be less hazardous in deep, non-CAA related ICH.

Key management strategies are avoidance of antiplatelet drugs and statins in those with CAA remains unclear.

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### Table 3: Classical and Modified Boston Criteria, table from [4]. Key differences between the Classical and Modified Criteria are highlighted in bold.

<table>
<thead>
<tr>
<th>Classical Boston Criteria</th>
<th>Modified Boston Criteria</th>
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<tbody>
<tr>
<td><strong>Definite CAA</strong></td>
<td>Full post-mortem examination demonstrating:</td>
</tr>
<tr>
<td></td>
<td>• Lobar, cortical or cortico-subcortical 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><strong>Probable CAA</strong></td>
<td>Clinical data and pathological tissue (either evacuated haematoma or cortical biopsy) demonstrating:</td>
</tr>
<tr>
<td></td>
<td>• Lobar, cortical or cortico-subcortical haemorrhage</td>
</tr>
<tr>
<td></td>
<td>• CAA within the specimen (any degree)</td>
</tr>
<tr>
<td></td>
<td>• Absence of another diagnostic lesion</td>
</tr>
<tr>
<td><strong>Probable CAA with supporting pathology</strong></td>
<td>Clinical data and MRI / CT demonstrating:</td>
</tr>
<tr>
<td></td>
<td>• Multiple haemorrhages restricted to lobar, cortical or cortico-subcortical regions (including cerebellar haemorrhage)</td>
</tr>
<tr>
<td></td>
<td>• Age ≥ 55 years</td>
</tr>
<tr>
<td></td>
<td>• Absence of other cause of haemorrhage</td>
</tr>
<tr>
<td><strong>Possible CAA</strong></td>
<td>Clinical data and MRI / CT demonstrating:</td>
</tr>
<tr>
<td></td>
<td>• Single lobar, cortical or cortico-subcortical haemorrhage</td>
</tr>
<tr>
<td></td>
<td>• Age ≥ 55 years</td>
</tr>
<tr>
<td></td>
<td>• Absence of other cause of haemorrhage</td>
</tr>
</tbody>
</table>

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### References

9. Ryan NS, Lashley T, Revesz T, Danzio D, Fox NC, Morris HR. Spontaneous ARIA (amyloid-related imaging abnormalities) and cerebral amyloid angiopathy related inflammation in premilary families. J. Alzheimer’s Dis., 2015;44:1069-74
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