Advances in our Understanding of the Pathophysiology, Detection and Management of Cerebral Amyloid Angiopathy

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Abstract

Cerebral amyloid angiopathy (CAA) is pathologically defined as the deposition of amyloid protein, most commonly the amyloid peptide (A), primarily within the media and adventitia of small and medium-sized arteries of the leptomeninges, cerebral and cerebellar cortex. This deposition likely reflects an imbalance between A production and clearance within the brain and leads to weakening of the overall structure of brain small vessels, predisposing patients to lobar intracerebral haemorrhage (ICH), brain ischaemia and cognitive decline. CAA is associated with markers of small vessel disease, like lobar microbleeds and white matter hyperintensities on magnetic resonance imaging. Therefore, it can be now be diagnosed during life with reasonable accuracy by clinical and neuroimaging criteria. Despite the lack of a specific treatment for this condition, the detection of CAA may help in the management of patients, regarding the prevention of major haemorrhagic complications and genetic counselling. This review discusses recent advances in our understanding of the pathophysiology, detection and management of CAA.

Cerebral amyloid angiopathy (CAA) is a disorder of the central nervous system characterised by the deposition of amyloid proteins in the wall of small- to medium-sized vessels, most frequently arteries, within the leptomeninges and cortex of the brain.[1] In vessels affected by CAA, local muscle and elastic elements of the arterial wall are lost and replaced by amyloid fibrils, primarily the amyloid- (A) peptide. Since the first description of neurovascular amyloid deposition in 1909 by Gustav Oppenheim, sound scientific evidence has supported the concept that the associated disruption of the overall structure of those small vessels predisposes to both ischaemic small vessel disease and cerebral haemorrhage.[2–4]

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Sporadic CAA is a major cause of lobar intracerebral haemorrhage (ICH) and cognitive decline in the elderly, including the normotensive population.[5,6] Hereditary forms of CAA are generally rare, usually more severe and earlier in onset. Rare non-A familial CAAs can also present clinically with lobar ICH.[7] Regarding sporadic CAA, two major challenges persist:

- a definitive diagnosis requires a neuropathological exam; and[8]

- no treatment or preventive strategy for CAA or CAA-ICH has been firmly established.

Nevertheless, in the last decades of research, there has been remarkable progress in our understanding of this condition. CAA pathology has been associated with markers of small vessel disease, including lobar cerebral microbleeds (CMB) and white matter hyperintensities on magnetic resonance imaging (MRI).[9–11] The availability of MRI sequences that are particularly sensitive to susceptibility effects like the T2* gradient-recalled echo (GRE) and susceptibility weighted imaging (SWI) now allow reliable assessment of an individual's haemorrhagic burden over time and reasonable accuracy by clinical and neuroimaging diagnostic criteria.[10–13] As our understanding of CAA pathophysiology evolves, specific targets have been identified as candidates for the prevention and treatment of this condition.[14] As new research tools such as the Pittsburgh Compound B (PiB) or other amyloid-imaging agents for positron emission tomography (PET) scan become incorporated into clinical practice, it may also be possible to detect vascular amyloid deposition in the brain noninvasively in living patients, perhaps before an ICH or significant cognitive decline.[15]

This article focuses on our current understanding of the pathophysiology of sporadic CAA, the new imaging modalities and laboratory biomarkers that may aid in its detection and the currently available evidence that could guide the management of patients with this condition.

Pathophysiology and Genetics of Sporadic Cerebral Amyloid Angiopathy

Sporadic CAA is the most frequent form of the disease, mostly occurring in the elderly and defined by the accumulation of A in the vessel walls of capillaries, arterioles and small and medium-sized arteries of the cerebral cortex, leptomeninges, and cerebellum. Sporadic CAA is not associated with other systemic, primary or secondary, amyloidosis.

The A peptide is the normal proteolytic product of the integral membrane protein A precursor protein (APP), encoded by the APP gene on chromosome 21.[16–19] A occurs as 40 or 42 amino acid species (A 40, A 42) and its generation from APP requires two enzymatic events: a proteolytic cleavage at the amino terminus of the A sequence by -secretase; and a cleavage at the carboxyl terminus by -secretase.[16–19] Via mechanisms that remain still unknown, soluble A forms undergo a change in conformation, resulting in a predominantly -sheet structure, highly prone to oligomerisation, fibrillisation and deposition. These deposits can trigger a secondary cascade of events that include release of inflammatory components, activation of the complement system, oxidative stress, alteration of the blood–brain barrier (BBB) permeability and cell toxicity.[20–22]

A in CAA is structurally similar to the peptide that constitutes senile plaques in Alzheimer's disease (AD). In contrast to Alzheimer plaques, however, a substantial proportion of vascular deposits in CAA is of the shorter A 40 species.[20] Increases in the A 40/42 ratio appears to favour vascular over parenchymal amyloid deposition.[22] The cascade of events that promotes cerebrovascular A accumulation is still not fully understood but an imbalance between A production and clearance is likely to play a key

role.[22] Deposited Aβ appears to derive from neurons although circulating Aβ may play a seeding function for brain deposition, since intraperitoneal inoculation with Aβ-rich extracts can induce CAA in transgenic mice over expressing APP.[22–25] Recent data from animal models indicate that ischaemic strokes may trigger accelerated amyloid build-up, most likely through interference with clearance pathways.[26]

The mechanism of blood vessel rupture in CAA is still under debate. Amyloid deposition has been associated with reduced vascular compliance, cracking and weakening of the vessel wall that predispose to vascular rupture and subsequent extravasation of blood to brain parenchyma.[27,28] The reason why some vessel ruptures lead to major lobar haemorrhage in CAA patients while others lead to microhaemorrhage may be related to differences in thickness of small vessel walls. Apparently, CAA patients with thicker vessel walls have more CMB and those with thinner walls are more prone to develop symptomatic lobar ICH.[29]

Pathology of Cerebral Amyloid Angiopathy

Pathological studies of CAA show that Aβ vascular deposits infiltrate the media and adventitia of the microvasculature, resulting in loss of smooth muscle cells with replacement of the vascular media and acellular thickening of the vessel wall.[30,31] Advanced CAA is characterised by severe disruption of the vascular architecture, that includes the distinctive 'vessel-within-vessel' appearance, microaneurysm formation, fibrinoid necrosis, hyaline degeneration, obliterative intimal changes and perivascular leakage of blood products.[30–32]

CAA distribution is characteristically patchy and segmental, involving predominantly the lobar areas.[8] For unknown reasons, CAA is most frequent in the occipital lobes. This contrasts with hypertensive arteriopathy, which is characterised by lipohyalinosis and fibrinoid necrosis of small deep perforating arteries and therefore typically affects deep brain structures including the basal ganglia, brain stem and thalamus.[33] Nevertheless, since over 30 % of patients with CAA-related ICH have documented arterial hypertension (HTN), some patients exhibit both hypertensive and CAA microvascular alterations.[3]

CAA pathology is common in the elderly, with a prevalence from 10–50 % of the general elderly population, in autopsy series.[34,35] Some CAA pathology is also present in nearly all brains with AD and advanced CAA is present in approximately 25 % of AD brains.[35,36] However, fewer than 50 % of CAA cases meet the pathological criteria for AD.[3]

Genetics of Sporadic Cerebral Amyloid Angiopathy

The apolipoprotein E (APOE) ε4 and ε2 alleles are genetic risk factors associated with risk of developing sporadic CAA-related ICH.[37,38] APOE ε2 exerts a protective effect on AD risk but increases risk of ICH in CAA patients.[39,40] The ε2 allele is predominantly associated with vasculopathic changes that predispose to rupture of the diseased vessels, whereas ε4 is related to the severity of amyloid deposition within the vessel wall.[41,42] Interestingly, recent studies have found that possession of APOE ε2 predisposes individuals with lobar ICH to haematoma expansion.[43,44] This effect was more pronounced in patients with amyloid angiopathy-related ICH, consistent with the ε2 allele's role in vascular amyloid deposition and vessel fragility. More recently, the CR1 gene has also been linked to risk of CAA-related ICH, recurrent CAA and CAA pathology burden.[45]

Detection of Cerebral Amyloid Angiopathy

Approximately 50 % of patients over 80 years of age display some pathological evidence of CAA, mostly without clinical symptoms. Among individuals with more advanced CAA, the clinical presentation can vary from incidental asymptomatic microbleeds on MRI to

catastrophic lobar ICH. Dementia, cognitive impairment and transient neurological symptoms or signs are also increasingly recognised.[46]

Primary lobar ICH is the most common clinical presentation leading to the diagnosis of CAA. HTN and CAA are responsible for most primary ICHs in the elderly. The clinical manifestations of CAA-related ICH are similar to other types of ICH. The signs and symptoms depend on the size and location of the bleed and may include headache, focal neurological deficits, seizures and altered level of consciousness.[45]

In a retrospective analysis of consecutive patients with non-traumatic SAH, CAA was found to be a common cause of SAH in the elderly and clinically presents with single or recurrent focal transient neurological events of short duration.[47] CAA has also been recognised as a probable cause of ischaemic small vessel disease.[48,49] Indeed, amyloid deposits can narrow the vessel lumen, impair cerebral blood flow regulation, cause alterations in endothelial structure and function and influence vessel dilation in response to physiologic stimuli.[50–52] Progression of CAA ischaemic burden may lead to cognitive decline and ultimately to vascular dementia.[53]

A subset of patients with CAA-related inflammation may present with subacute cognitive decline, seizures and diffuse radiographic white matter abnormalities attributed to vasogenic oedema.[54,55] The APOE 4/ 4 genotype has been associated with CAA-related inflammation and evidence of CAA-related vasculitis or perivascular inflammation on pathologic examination.[56]

Histological Diagnosis

Definitive diagnosis of CAA requires histopathological exam. Congo red staining for amyloid under light microscopy (see Figure 1A) has been the classical method for amyloid staining, although its sensitivity is relatively low.[57] Immunohistochemistry with fluorescent antibodies specific for A (see Figure 1B) is increasingly used to identify amyloid accumulation in the brain.

Neuroimaging

MRI sequences that are particularly sensitive to susceptibility effects like GRE and SWI can identify not only major bleeding in the brain but also CMBs, which may not be visible on other imaging modalities (see Figure 2).[12,58] CMBs have hypointense signal on GRE sequences due to haemosiderin, a blood breakdown product that causes magnetic susceptibility-induced dephasing, leading to T2* signal loss. The appearance of microbleeds on GRE sequences is larger than the actual tissue lesions because of the so-called blooming effect of the magnetic resonance signal at the border of these lesions.[12,57,58] Novel techniques such as SWI have considerably increased microbleed detection rates.[59–61]

The ability of MRI to detect CMBs has greatly aided the non-invasive diagnosis of CAA during life. As haemosiderin remains in macrophages for many years after haemorrhage, MRI sequences that are particularly sensitive to susceptibility effects allow for reliable assessment of an individual's haemorrhagic burden over time. Haemorrhage burden identified by MRI predicts clinically important events in survivors of lobar ICH.[62] Detection of microhaemorrhages is therefore useful for assessing risk of functional deterioration in CAA patients as well as for risk of future ICH.[62] It is noteworthy that CAA-related CMB, like CAA pathology and CAA-related-ICH, tend to cluster in posterior brain regions.[60]

Non-traumatic subarachnoid haemorrhage (SAH) and superficial siderosis are also common in patients with CAA.[63,64] Superficial siderosis may be found at sites distant from ICH and

in close vicinity to lobar CMBs, suggesting that SAH can also occur as a primary manifestation of CAA.[65–67]

Boston Criteria

Using a combination of clinical, neuroimaging and pathological data, the Boston criteria establish three levels of certainty for the diagnosis of CAA: definite, probable and possible. These criteria were based on the tendency for CAA-related haemorrhages to occur in elderly patients, to be multiple and primarily located in lobar brain regions.[13] As fully described in Table 1, the diagnosis of probable or possible CAA can be reached by clinical and neuroimaging findings alone without requiring pathological confirmation.[13,68] The modified Boston criteria include superficial siderosis as one of the required lobar haemorrhagic lesion, which has been reported to improve the sensitivity of the diagnosis without lowering its specificity (see Figure 3).[64]

Positron Emission Tomography Imaging

PET imaging with Pittsburgh compound B (PiB) has been used in research to measure the burden and location of brain fibrillar A deposits in animal models and in humans with AD or CAA.[15,69–72] Global PiB retention is elevated in non-demented CAA subjects relative to healthy control subjects (see Figure 4), although lower in CAA than in AD subjects.[3] Importantly, the occipital-to-global PiB ratio was found to be significantly greater in CAA than in patients with AD.[15] Increased occipital PiB retention was further demonstrated in a young subject with early Iowa-type hereditary CAA, a rare hereditary form of CAA in which the fibrillar amyloid deposits appear to be entirely vascular.[73] Taken together, these results suggest that PiB-PET can noninvasively detect CAA, possibly prior to overt signs of tissue damage such as haemorrhage or white matter lesions.

At present, PiB-PET use is still considered investigational by the FDA for the diagnosis of AD or CAA. Other amyloid-binding compounds using the longer-lasting radionuclide fluorine-18 have more recently been tested to detect amyloid and may enter into clinical practice.[74]

Cerebrospinal Fluid Biomarkers

Patients with AD have decreased cerebrospinal fluid (CSF) concentrations of A 42 protein and increased tau protein, which allows reasonably accurate differentiation between AD patients and controls (sensitivity and specificity generally >80 %).[75–83] More recently, CSF concentrations of both A 42 and A 40 were shown to be reduced in non-demented CAA subjects compared to both healthy controls and AD subjects.[83] These results suggest that the large component of A 40 deposited in vessels in advanced CAA may deplete this peptide from CSF, similarly to AD-associated reductions of A 42. Total and phosphorylated tau protein levels were not significantly different in CAA from controls. The combination of A 42 and total tau strongly discriminated CAA from controls (area under the receiver operator curve, 0.98), although discrimination between CAA and AD was less distinct (area under the receiver operator curve, 0.82).[83] Taken together, these data suggest that A 40, A 42, and tau protein levels in the CSF may be useful biomarkers of advanced CAA pathology.

Management of Patients with Cerebral Amyloid Angiopathy

There is no evidence-based treatment or preventive strategy specific for CAA or CAA-related ICH at this time. Given the increased risk of a first or recurrent ICH or progressive cognitive decline, the clinical diagnosis of CAA may nonetheless have impact on the management of some patients, especially regarding the use of anti-thrombotic medications,

management of co-morbidities, long-term prognosis, cognitive follow-up and genetic counselling. Furthermore, patients who present with CAA-related inflammation have a potentially treatable form of the disease because of its responsiveness to immunosuppressive therapy.

Anti-thrombotic Medications

Anticoagulation with warfarin increases mortality after ICH and may not be safe following CAA-related ICH.[84] While selected patients with deep hemispheric ICH at particularly high risk for thromboembolic stroke and low risk of ICH recurrence might benefit from long-term anticoagulation, patients with CAA-related ICH and atrial fibrillation should not be offered long-term anticoagulation.[84] A small case-control study found an association between the presence of CMBs and warfarin-related ICH,[85] but the relative risks and benefits of anticoagulation in patients with CMBs are less clear. At least two observational studies found that antiplatelet therapy increased the risk of recurrent CAA-related ICH, particularly for individuals with larger numbers of microbleeds.[86,87] Larger, more definitive studies are required to settle these important questions, which could have considerable clinical implications.

Management of Co-morbidities

In the Perindopril protection against recurrent stroke study (PROGRESS), blood pressure lowering treatment using perindopril plus optional indapamide was found to provide protection against both ischaemic and haemorrhagic stroke.[88] Further *post hoc* analysis indicated that randomisation to the blood pressure-lowering regimen reduced risk for CAA-related ICH in particular, suggesting that blood pressure reduction may have benefits in this population.[89]

Management of Cerebral Amyloid Angiopathy-related Intracerebral Haemorrhage

There is no evidence that the acute medical management of patients with CAA-associated ICH should differ from other causes of ICH.[90] A subgroup analysis of the Surgical trial in intracerebral haemorrhage (STICH) II suggested better functional outcomes after surgery in patients with superficial as well as lobar ICH in the absence of IVH.[91] The ongoing STICH II will specifically test the benefits of early surgical evacuation for lobar haematomas within 1 cm of the cortical surface without intraventricular extension.[92] The results of this trial will have particular bearing on the surgical management of patients with CAA-related ICH, as lobar ICH is the hallmark of this condition.[93]

Management of Inflammatory Cerebral Amyloid Angiopathy

The inflammatory presentation of CAA represents a potentially treatable form of the disease. Corticosteroid treatment has been shown in some case reports and small series to ameliorate symptoms associated with CAA-related inflammation, possibly by reducing vasogenic oedema.[94] Other immunosuppressant treatments have been reported to influence the course of inflammatory CAA, but available evidence is limited.[95] DiFrancesco and colleagues reported a patient with CAA-related inflammation who was found to have elevated auto-antibodies to A 40 and A 42 in CSF with subsequent reductions following corticosteroid treatment, offering a potential biological mechanism for this syndrome.[96] If this finding can be confirmed, titres of CSF anti-A antibodies might serve as a biological marker for the diagnosis, monitoring and evaluation of treatment in CAA-related inflammation.

Genetic Testing and Counselling

The over-representation of the APOE 2 allele in patients with warfarin-associated lobar ICH highlights a future potential for identifying high-risk patients for anticoagulation.[97] The

APOE 2 allele has also been associated with larger baseline ICH volumes, haematoma expansion, presence of spot sign on initial CT angiography and poor outcome in lobar ICH.[43,44] Nevertheless, there is currently not enough scientific evidence to support routine APOE genotyping of CAA patients for clinical purposes out of an investigational protocol.[98,99]

Mutations of APP as well as other genes unrelated to A such as cystatin C, BRI and transthyretin have been associated to familial CAA.[100–105] Interestingly, different carriers of the same mutation may have dramatically different clinical presentationss.[105] Genetic testing and counselling may be appropriate to patients with a strong family history of lobar ICH or vascular dementia. When faced with those uncommon cases, it is reasonable to offer referral to an academic research centre for further genetic evaluation, differential diagnosis and follow-up.

Conclusions

Since the original description of neurovascular amyloid deposits in 1909, there has been remarkable progress in our understanding of CAA. A definitive diagnosis still relies on histopathological evaluation but MRI sequences now allow reliable assessment of an individual's haemorrhagic burden over time and reasonable diagnostic accuracy via clinical neuroimaging. CAA has been associated with both ischaemic and haemorrhagic manifestations within the brain and is a major cause of lobar ICH and cognitive decline in the elderly. Despite the absence of specific treatment for this condition, the clinical diagnosis of CAA may have a significant impact on the management of some patients, especially regarding the use of antithrombotic medications, management of co-morbidities, long-term prognosis, cognitive follow-up and genetic counselling.

Acknowledgments

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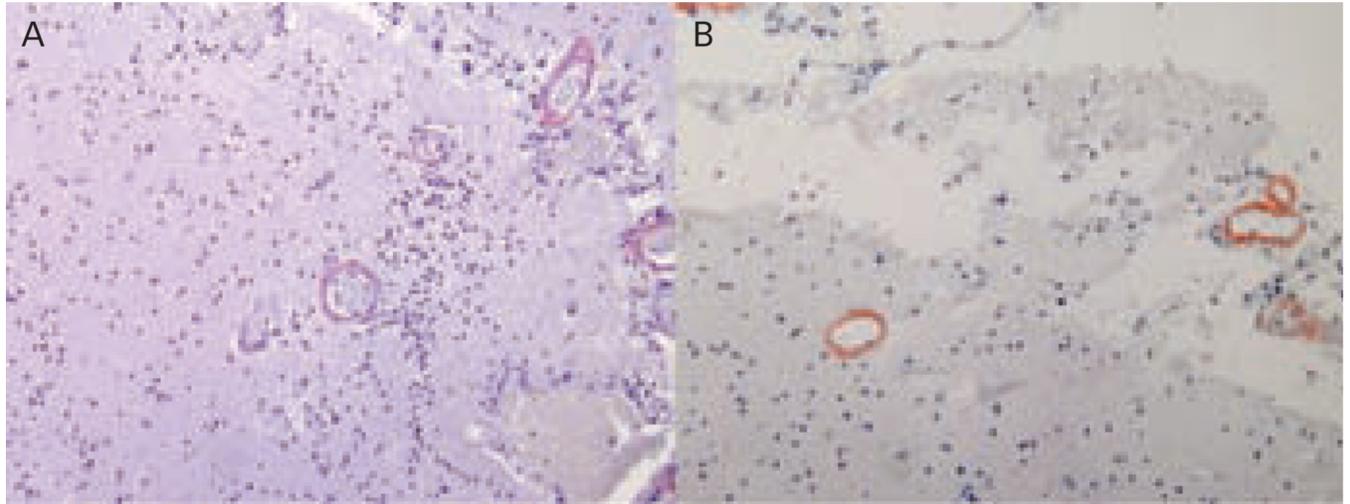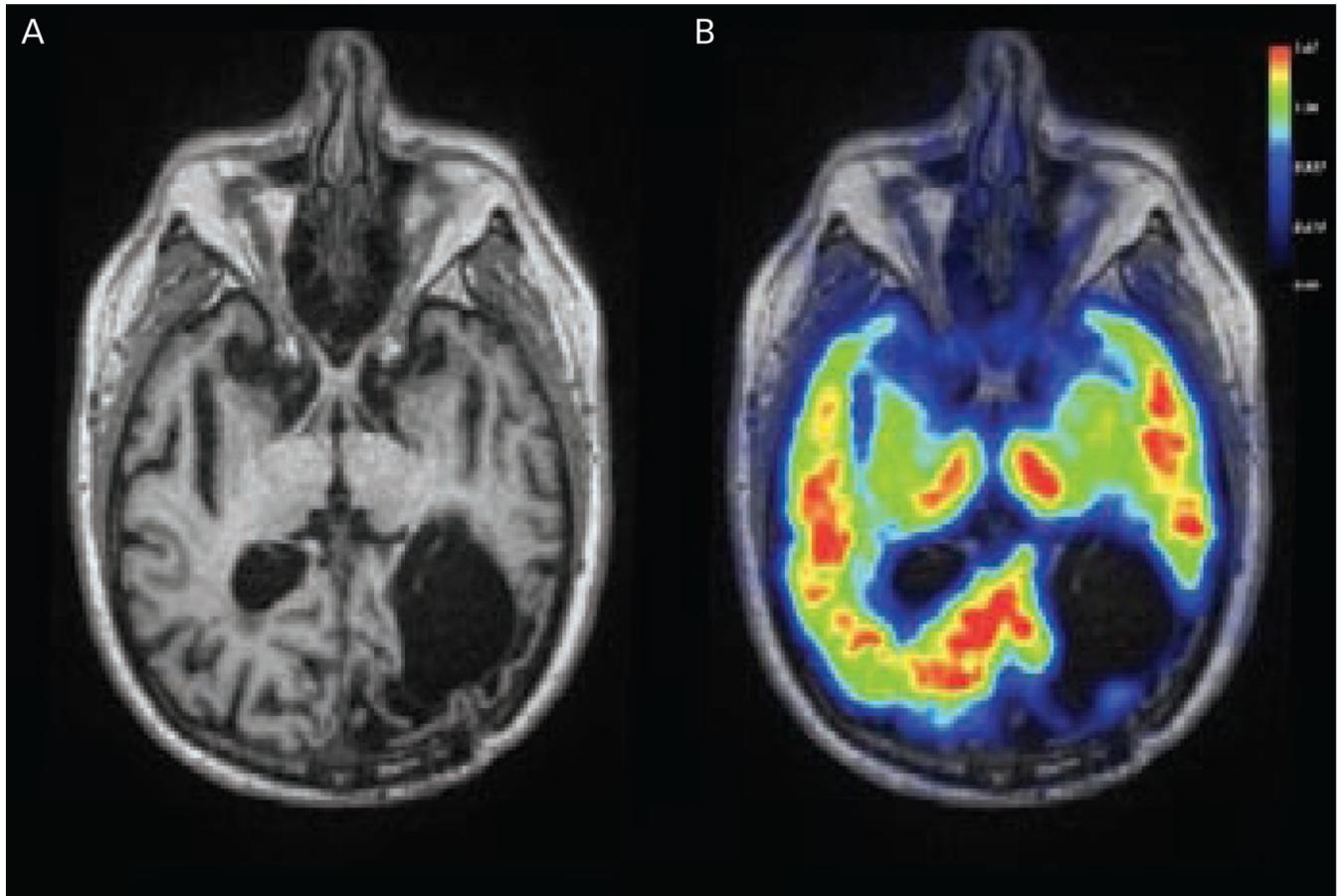
Figure 1.
Histopathological Sections from a Patient with Definite Cerebral Amyloid Angiopathy Confirmed by Congo Red Stain (A) and Immunostaining (B), Demonstrating Vascular Amyloid Deposition
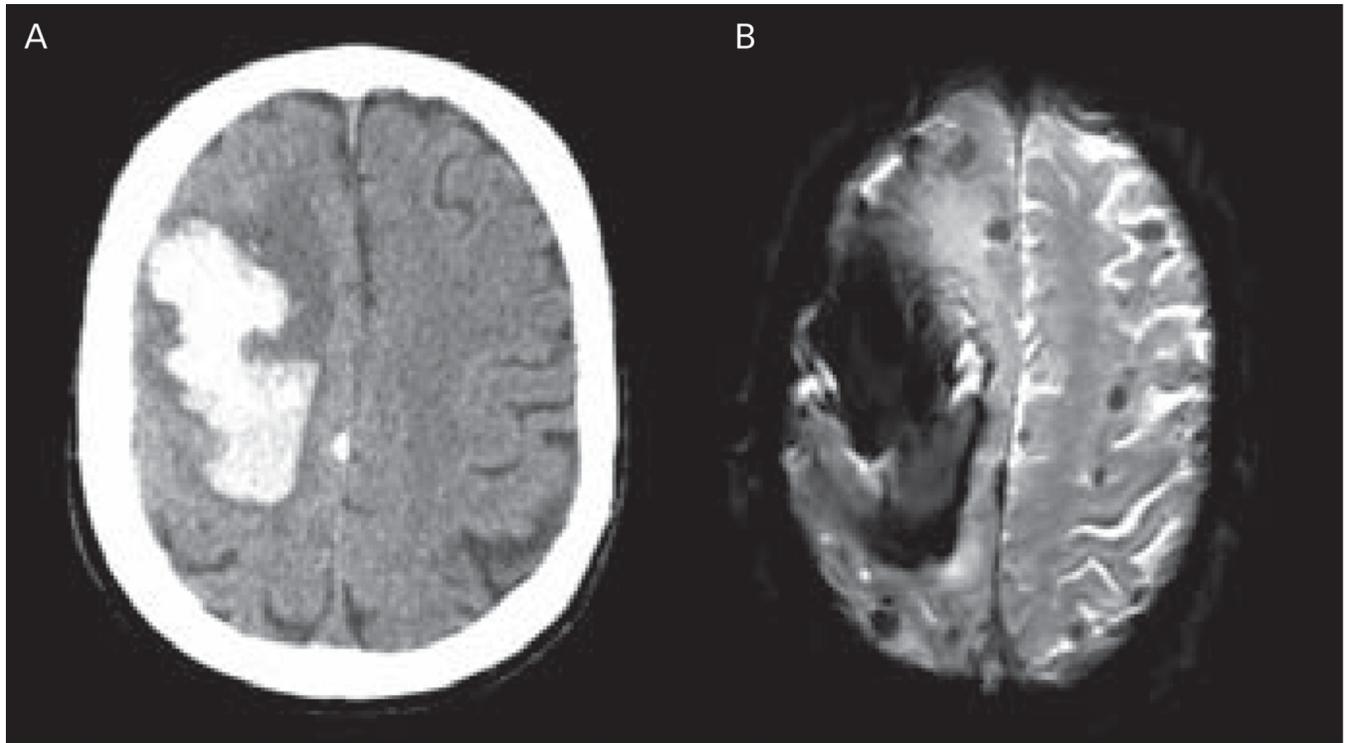
Figure 2.
Neuroimaging of a Patient with Probable Cerebral Amyloid Angiopathy-related
Intracerebral Haemorrhage, According to the Boston Criteria
A: Computed tomography (CT) scan showing large right frontal intracerebral haemorrhage
(ICH); B: magnetic resonance imaging (MRI) gradient recalled echo (GRE) sequence
showing the large frontal lobar haematoma and several additional lobar microbleeds.
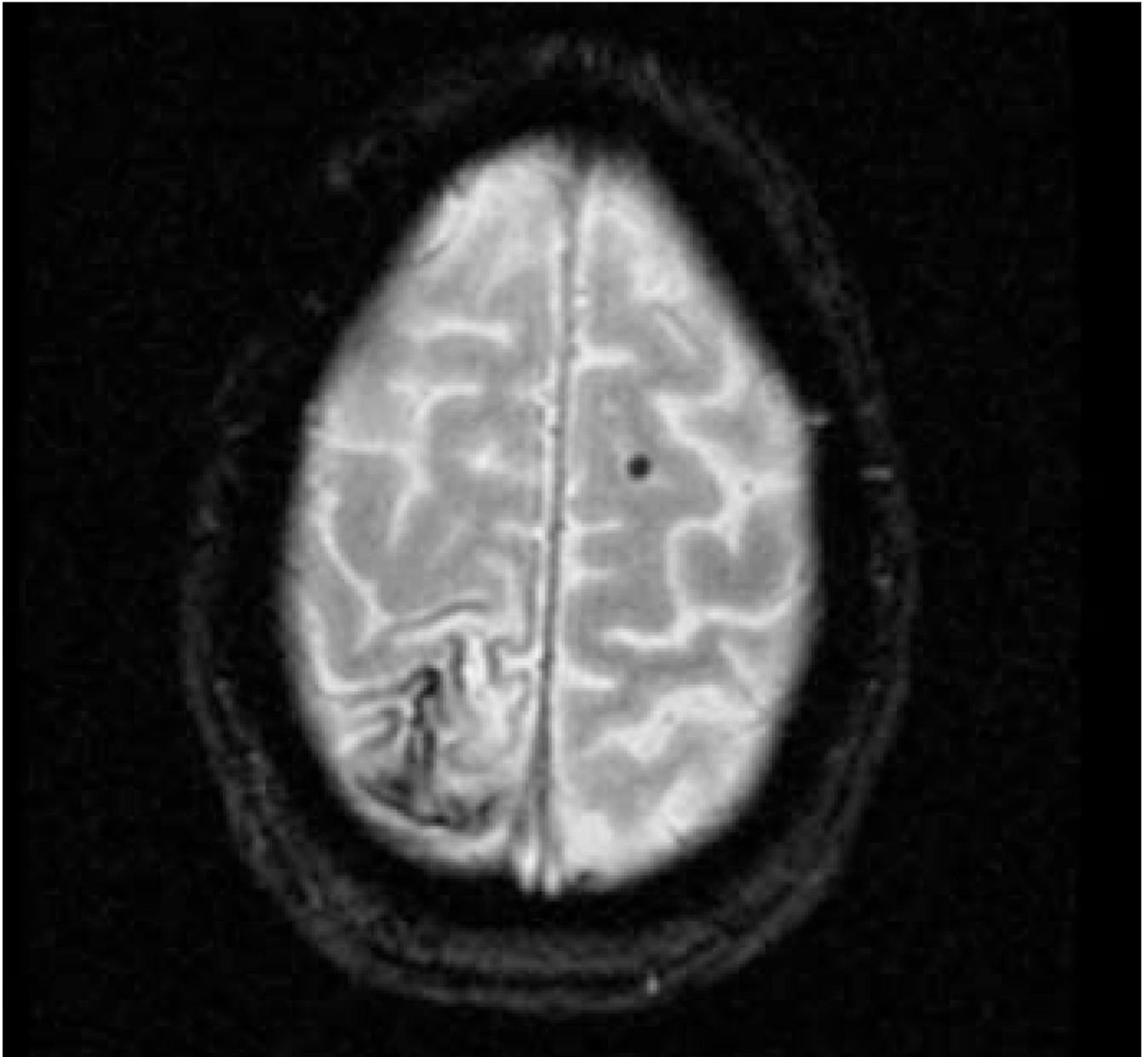
Figure 3.
Patient with Probable Cerebral Amyloid Angiopathy According to the Modified Boston Criteria
Gradient recalled echo (GRE) showing cortical siderosis on the right parietal lobe and a lobar microbleed on the left frontal lobe.

Figure 4.
Pittsburgh Compound B Positron Emission Tomography Scan of a Patient with Definitive
Cerebral Amyloid Angiopathy Subsequently Confirmed at Autopsy
A: Magnetic resonance image (MRI) T1 showing encephalomalacia from a previous left
occipital intracerebral haemorrhage (ICH). B: Pittsburg compound B (PiB) positron
emission tomography (PET) scan co-registered to MR showing increased PiB retention in
the posterior regions of the brain, including right occipital and bilateral temporal cortex.

Table 1

Boston Criteria for Cerebral Amyloid Angiopathy Diagnosis

1 Definite Cerebral Amyloid Angiopathy (CAA)

Full *post-mortem* examination demonstrating:

- lobar, cortical or corticosubcortical 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 corticosubcortical haemorrhage
- some degree of CAA in specimen
- absence of other diagnostic lesion

3 Probable CAA

Clinical data and MRI or CT demonstrating:

- multiple haemorrhages restricted to lobar, cortical or corticosubcortical regions (cerebellar haemorrhage allowed)
- age 55 years
- absence of other cause of haemorrhage [*]

4 Possible CAA

Clinical data and MRI or CT demonstrating:

- single lobar, cortical or corticosubcortical haemorrhage
- age 55 years
- absence of other cause of haemorrhage [*]

[*] Other causes of intracerebral haemorrhage include: excessive warfarin dosing (international normalised ratio [INR] >3.0), antecedent head trauma or ischaemic stroke, central nervous system (CNS) tumour, vascular malformation, CNS vasculitis, blood dyscrasia, coagulopathy.

CT = computed tomography; MRI = magnetic resonance imaging.