Published in final edited form as:
Ann Neurol. 2011 December ; 70(6): 871–880. doi:10.1002/ana.22516.

Cerebral Amyloid Angiopathy in the Elderly

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Abstract

Cerebral amyloid angiopathy (CAA) results from deposition of β-amyloid in the media and adventitia of small arteries and capillaries of the leptomeninges and cerebral cortex and is a major cause of lobar intracerebral hemorrhage and cognitive impairment in the elderly. CAA is associated with a high prevalence of magnetic resonance imaging markers of small vessel disease, including cerebral microbleeds and white matter hyperintensities. Although advanced CAA is present in approximately ¼ of brains with Alzheimer disease (AD), fewer than half of CAA cases meet pathologic criteria for AD. This review will discuss the pathophysiology of CAA and focus on new imaging modalities and laboratory biomarkers that may aid in the clinical diagnosis of individuals with the disease.

Cerebral amyloid angiopathy (CAA) is a major cause of lobar intracerebral hemorrhage (ICH) and cognitive impairment in the elderly and is associated with a high prevalence of markers of small vessel disease, including white matter hyperintensities and cerebral microbleeds.[1]

CAA is the most common cause of lobar intracerebral hemorrhage (ICH) in the elderly and results from cerebrovascular deposition of β-amyloid protein.[2,3] CAA is present in nearly all brains with Alzheimer disease (AD),[4] and advanced CAA is present in approximately 25% of AD brains.[5] This may suggest a common β-amyloid– based pathogenesis for these diseases. However, despite the close molecular relationship between the 2 diseases, CAA remains a clinically distinct entity from AD. Fewer than 50% of CAA cases meet the pathologic criteria for AD.[2,3] Furthermore, >75% of patients with AD have only mild or no CAA.[5]

This review will discuss the pathophysiology of CAA and focus on new imaging modalities and laboratory biomarkers that may aid in the clinical diagnosis of individuals with the disease. Future areas of research will also be discussed.

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Potential Conflicts of Interest

A.V. has served as a consultant for Athena Diagnostics and has grants/grants pending from the NIH. S.M.G. has served as a consultant for Hoffman-La Roche, Janssen Alzheimer Immunotherapy, and Bristol-Myers Squibb Company and has received honoraria from Medtronic and Pfizer.

Vascular Pathophysiology and CAA-Related Brain Injury

Sporadic CAA is characterized by deposition of β-amyloid in the media and adventitia of small arteries and capillaries of the leptomeninges and cerebral cortex. The occipital regions are preferentially affected for unclear reasons. In contrast to Aβ deposition in AD, a substantial proportion of Aβ in vascular deposits is the shorter Aβ40 species.[6] Accelerated vascular deposition of Aβ may occur through transcriptional regulation of the lipoprotein receptor LRP in vascular smooth muscle due to overexpression of the transcription factors serum response factor (SRF) and myocardin.[7] Additionally, SRF and myocardin may also regulate contractile proteins in vascular smooth muscle cells, thus altering normal vessel physiology.[8]

Although the exact source of vascular amyloid has not been elucidated, it has been suggested to be predominantly generated by neurons and subsequently deposited in the vessel wall.[9] Transgenic mouse models suggest that amyloid expressed in neurons can generate CAA,[6,10] with possible additional contribution from ineffective transport of Aβ out of the central nervous system.[7,11–13] An alternative or complementary mechanism is the possible role of peripheral Aβ in the development of CAA and Aβ-related brain pathology, as recently highlighted in a transgenic mouse model.[14] There is some evidence to suggest that the liver may be a source of Aβ.[15] Indeed, Aβ in circulating plasma may be an important precursor pool for brain Aβ, as it has been shown to cross the blood–brain barrier in a variety of animal models.[16–22]

Pathological examination of blood vessels in both sporadic and familial CAA show loss of smooth muscle cells, vessel wall thickening, lumenal narrowing, concentric splitting of the vessel wall, microaneurysm formation, and perivascular microhemorrhage.[3,23–28] These results have been further extended to animal models of CAA.[6,29–33] Even in mildly affected transgenic mice overexpressing mutant forms of amyloid precursor protein, Aβ deposition has been shown to affect resting vessel diameter[27,34] and influence vessel dilatation in response to physiologic or pharmacologic stimuli.[30,35–37] There appears to be decreased cortical vascular reactivity to carbon dioxide and whisker stimulation proportional to the severity of vascular amyloid.[38]

In line with these animal studies, there is evidence to suggest that Aβ vessel pathology may have similar effects in patients with CAA. In Dutch-type hereditary CAA, the presence of dementia is be predicted by the amount of severely stenotic amyloid-laden vessels (as opposed to the severity of AD pathology).[39] More recent evidence has further suggested that amyloid deposition may also be associated with capillary vessel occlusion.[40] Furthermore, decreased vascular reactivity in response to visual stimulation has recently been found in a small cohort of CAA subjects. This potentially reflects the occipital predilection of the disease.[41]

CAA-related impairments of perfusion may be responsible for the subcortical white matter lesions and tissue microstructural changes seen in the disease.[42–45] Studies have suggested that advanced CAA is associated with a large burden of white matter lesions compared to healthy elders[44] or patients with AD alone.[45] Furthermore, damage to white matter in CAA

is associated with cognitive impairment independent of the effects of the brain hemorrhage.[42,43] Although CAA-related white matter hyperintensities preferentially affect the same periventricular regions affected by hypertensive small vessel disease,[46] there is some suggestion that at least a subgroup of patients with CAA demonstrate predominantly posterior white matter involvement.[47]

Pathologic studies suggest that cortical microinfarctions are common in CAA, with reported frequencies ranging from 37% to nearly 100%.[48–53] These microinfarctions are frequently multiple and are located in the cortical ribbon or underlying subcortical white matter. These microinfarctions may be related to impaired cerebral blood flow regulation in CAA[38,41] due to smooth muscle degeneration and capillary occlusion.[40] Recent studies have demonstrated that small diffusion-weighted imaging (DWI)-hyperintense lesions suggestive of subacute ischemic infarction are not infrequent in patients with CAA, occurring in approximately 15% of these patients.[54,55] Their presence appears to be unrelated to conventional vascular risk factors, but instead is associated with the number of hemorrhagic lesions on gradient echo (GRE) magnetic resonance imaging (MRI), a marker of CAA severity.[54] These lesions appear to be clinically silent events that occur as part of the ongoing pathogenesis of CAA. The signal characteristics, size, and location of these DWI-positive lesions suggest they may represent the neuroimaging correlates of the neuropathologic infarctions described in association with CAA.[48–52] Given the transient appearance of DWI-positive signal after stroke, the finding of these DWI-positive lesions in 15% of subjects suggests these small infarctions may occur at a very high frequency. Based on this, and assuming a 10-day postinfarction period where diffusion changes remain visually detectable on DWI,[56] their estimated annual prevalence would be approximately 8 new infarctions per person-year.[54] This estimate is strikingly high relative to the estimated incidence of new microbleeds (~1.4 per year) or symptomatic ICH (~0.14 per year) calculated from other cohorts with advanced CAA.[57] This suggests that the lifetime burden of ischemic infarction in advanced CAA could be substantial.

The genetic abnormalities underlying sporadic CAA have not been fully elucidated, although several inherited familial forms of CAA have been described.[58] The only specific genetic risk factor consistently identified for the sporadic disease has been the apolipoprotein E (APOE) genotype as a risk for CAA-related ICH.[59–61] In a population-based study, the presence of either APOE $\varepsilon 2$ or $\varepsilon 4$ alleles increased the risk of lobar ICH (odds ratio, 2.3; 95% confidence interval, 1.2–4.4).[59] Furthermore, the presence of the $\varepsilon 2$ or $\varepsilon 4$ alleles of the apolipoprotein E gene is associated with an increased risk of recurrent lobar ICH (28% cumulative recurrence rate at 2 years compared to 10% in lobar ICH patients without either allele).[62] The APOE $\varepsilon 2$ and $\varepsilon 4$ alleles have also been associated with an earlier age of onset of lobar hemorrhage. [63,64] Pathological studies have demonstrated that the $\varepsilon 2$ allele may promote steps in CAA-related vessel breakdown including wall splitting, microhemorrhage, and fibrinoid necrosis,[63,65] whereas APOE $\varepsilon 4$ is associated with a dose-dependent increase in the amount of vascular amyloid.[66–68] In contrast, in AD, APOE $\varepsilon 4$, but not APOE $\varepsilon 2$, is an established risk factor for late onset disease.[69,70] Individuals with the APOE $\varepsilon 4$ allele appear to have earlier onset and more rapid progression of AD-

associated pathology.[69,71] A current hypothesis suggests APOE ε4 may increase β-amyloid aggregation, impair β-amyloid clearance, or both.[71]

Cerebral Microbleeds and Significance in Sporadic CAA

Cerebral microbleeds were first described after the clinical use of GRE or T2*-weighted MRI.[72–74] Old and recent cerebral hemorrhages can be detected with high sensitivity using this technique.[73,74] The hypointense signal on GRE sequences is caused by hemosiderin, 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.[75,76] GRE MRI can detect millimeter-sized paramagnetic blood products (including hemosiderin) in brain parenchyma.[77] As hemosiderin remains in macrophages for many years after hemorrhage, [78,79] GRE sequences allow for reliable assessment of an individual's hemorrhagic burden over time. Furthermore, more recent technical advances in MRI software and hardware have yielded significant improvements in sensitivity, which have lead to increased detection of microbleeds in different populations.[80–82] For example, novel techniques such as susceptibility-weighted imaging have considerably increased microbleed detection rates.[57,74,80,81] Slice thickness and magnetic field strength may also influence detection rates.[81] Older studies employing GRE, larger slice thickness, or lower magnetic field strength may have failed to detect microbleeds that would have been visualized with these higher resolution techniques. Microbleed detection does not appear to vary greatly based on choice of precise size parameters.[83]

Lobar microbleeds in CAA are likely caused by vessel fragility and rupture due to the deposition of amyloid within the media and adventitia of small- to medium-sized cerebral arteries[3] and have been extensively studied in CAA.[57,78] A set of validated criteria (termed the Boston criteria) have been established to diagnose CAA during life.[84] The presence of multiple, strictly lobar hemorrhages (including microbleeds) detected by GRE MRI sequences has been shown to be highly specific for severe CAA in elderly patients with no other definite (Fig 1) cause of ICH, such as trauma, ischemic stroke, tumor, coagulopathy, or excessive anticoagulation (termed probable CAA-related ICH).[84,85]

Similar to the distribution of CAA pathology[86] and CAA-related lobar macrohemorrhages,[87,88] the distribution of microbleeds in CAA seems to show a posterior cortical predominance.[89] In a study of patients with probable CAA, microbleeds occurred more frequently in the temporal and occipital lobes compared to other hemispheric regions. Additionally, lesions tended to cluster in the same lobe in subjects with multiple lesions.[89]

Microbleeds located in the lobar regions in CAA have been shown to be related to disease progression, recurrent ICH, and CAA-related impairment.[57,85] In elderly patients (≥55 years old) presenting with lobar ICH, microbleeds appear >2× more frequently than macrohemorrhages.[57] Among patients who underwent an MRI 16-months later, 50% experienced new, frequently multiple microbleeds. Large number of microbleeds at baseline and APOE ε2 or ε4 genotype were the only predictors of new microbleeds. Both the number of hemorrhages at baseline and the number of new microbleeds at follow-up increased the

risk of recurrent hemorrhage (3-year cumulative risk, 14%, 17%, 38%, and 51% in subjects with 1, 2, 3–5, or ≥6 baseline hemorrhages, respectively). The distribution of new microbleeds at follow-up has been correlated with the distribution of baseline microbleeds.[89] In those who experienced recurrent lobar ICH, the location of hematoma was positively associated with the distribution of baseline hemorrhages (including microbleeds). The number of baseline hemorrhages was also associated with increased incidence of cognitive impairment, functional dependence, or death at follow-up (mean follow-up, 27.9 months; hazard ratio, 1.9).[57]

The precise relationship between microbleeds and macrobleeds in CAA remains an active area of investigation. A recent study has suggested that CAA subjects with very high (>50) microbleed counts have increased vessel wall thickness compared to those with relatively few (<3) microbleeds.[90] This suggests that increased wall thickness may predispose vessels to microbleeding when they rupture. In support of this hypothesis, severe wall thickening occurs in Iowa-type hereditary CAA, which is characterized by multiple microbleeds without symptomatic hemorrhage.[23] Although increased vessel wall thickness and luminal narrowing in patients with CAA is a well-described phenomenon,[24,91] little is known regarding the factors that determine degree of vessel wall thickness and how this relates to clinical impairment in the disease.[27]

CAA and AD

Neuropathological studies suggest that vascular and parenchymal Aβ deposits can occur either relatively independently of each other, or can overlap. The characteristics features of cerebrovascular and parenchymal Aβ deposition are summarized in Table 1. Of those individuals who die of CAA-related hemorrhage, approximately 50% meet AD criteria; approximately 25% of patients with AD also have severe CAA.[4,5] Neuroimaging evidence further supports these neuropathological findings. Particularly striking is the recent observation of lobar microbleeds— a hallmark feature of CAA—in $\frac{1}{5}$ or more of patients diagnosed with AD.[92–96] Microbleed prevalence has been reported to range from 15 to 32% of AD patients presenting to memory disorders clinics (Table 2). Evidence suggests that both prevalence and number of microbleeds in subjects with AD[93] are significantly higher than those reported in healthy populations.[97,98] Furthermore, microbleeds are considerably more prevalent in AD compared to many other causes of dementia, such as frontotemporal dementia, corticobasal degeneration, dementia with Lewy bodies, and progressive supranuclear palsy.[93]

The presence of CAA in patients with AD may also have important clinical relevance. This possibility is supported by clinical–pathological studies showing independent contributions of small vessel disease[99,100] and CAA in particular[101,102] to impairment in AD during life. This suggests that vascular brain injury acts additively or synergistically with concomitant AD pathology to produce more severe cognitive dysfunction than either process alone. This interpretation is supported by extensive clinical–pathologic data indicating that subjects with both vascular disease and AD pathology show either more severe cognitive impairment during life than those with pure AD[100,103,104] or require less severe AD pathology to produce the same amount of cognitive impairment. [105–107] Most of the vascular lesions

described in these studies were lacunar infarcts or microinfarcts rather than large territorial infarctions, supporting the importance of small vascular lesions also noted in population-based clinical–radiographic studies.[108,109] The possibility of synergistic interaction between AD and microvascular pathology is particularly relevant to the potential cognitive effects of CAA, which occurs preferentially in conjunction with AD pathology.[4,5,86]

CAA may be the basis of the inflammatory response that halted a phase IIa trial of active Aβ42 immunization in AD.[110] Both autopsied cases[111,112] of subjects who died from this experimental treatment demonstrated advanced CAA and perivascular inflammation similar to spontaneous CAA-related inflammation.[113] Further support for the possible role of CAA as trigger for the vaccine-associated reaction comes from the clinical, neuroimaging, and neuropathologic similarities between this syndrome and a spontaneous form of CAA-associated vascular inflammation.[113,114] Most recently, MRI changes similar to those in CAA-associated vascular inflammation have been reported in early trials of passive anti-Aβ immunization in 3 subjects and associated cognitive changes in 1,[115] suggesting that CAA remains an important obstacle even for passive immunotherapy and highlighting the potential importance of identifying AD subjects with accompanying CAA.

CAA in the General Population

Several recent studies in population-based cohorts have suggested that lobar cerebral microbleeds are common in healthy elderly individuals.[82,116] For example, Vernooij et al found that microbleeds were present in >30% of individuals aged >70 years,[82] the majority with a strictly lobar microbleed distribution. Individuals with the *APOE ε4* allele were more likely to have lobar microbleeds. Although further studies are necessary, these data may suggest that there may be a large number of asymptomatic elders with CAA in the general population and raise the eventual possibility of identifying these individuals early in their clinical course, before they experience a devastating lobar ICH or cognitive impairment.

The presence of CAA in the general population may have an independent impact on the cognitive status of elders. In this issue of *Annals of Neurology*, Arvanitakis et al[117] examine the relationship between CAA and cognitive impairment in community-dwelling elders from the clinicopathologic Religious Orders Study. They show that CAA is very common in this population, occurring in nearly 85% of subjects, and that CAA pathology is correlated with AD pathology. Multivariate analyses controlling for AD pathology and other potential confounding variables demonstrate that individuals with moderate-to-severe CAA have lower perceptual speed and episodic memory. These interesting results suggest that CAA pathology affects specific cognitive domains independently from AD pathology.

Other Methods of CAA Detection

Pittsburgh Compound B–Positron Emission Tomography Imaging

MRI detection of CAA-associated hemorrhages has proven extremely useful as a pathologically validated technique for diagnosing CAA during life. This approach is fundamentally limited, however, to detecting the pathologic effects of advanced CAA rather than the vascular amyloid itself.

An emerging technique is positron emission tomography (PET) imaging with Pittsburgh compound B (PiB) to measure the burden and location of fibrillar Aβ deposits. [118–122] In a recent study, a group of CAA subjects were compared with a group of probable AD subjects and a group of older normal control subjects. Global PiB retention in the nondemented CAA subjects was significantly increased in CAA relative to healthy control subjects ($p = 0.0009$), although lower in CAA than in AD subjects ($p = 0.002$) (example shown in Fig 2, left panel). Importantly, the occipital-to-global PiB ratio was found to be significantly greater in CAA than AD ($p = 0.003$) (see Fig 2, right panel).[121] In addition to being able to detect the parenchymal Aβ deposits in AD, PiBPET appears to be able to specifically detect CAA pathology, as recently shown in Iowa-type hereditary CAA.[123]

CSF Biomarkers

There is convincing evidence to suggest that Aβ protein in cerebrospinal fluid (CSF) may serve as biomarkers in the diagnostic workup of dementia patients and may be able to reliably distinguish patients with AD pathology. [124–129] Patients with AD have consistently been shown to have decreased CSF concentrations of Aβ42 and increased tau protein.[124,130,131] Therefore, measurement of CSF concentrations Aβ and tau protein potentially allows highly accurate differentiation between AD patients and controls (sensitivity and specificity generally >80%).

More recently, differences in Aβ40 and Aβ42 levels between healthy elderly subjects and patients with either AD or CAA have been investigated.[132] Whereas concentrations of Aβ42 were reduced in both the AD and the CAA groups, Aβ40 levels were also lower in CAA compared to both the healthy controls and the AD subjects. These results are consistent with the hypothesis that the large component of Aβ40 deposited in vessels in advanced CAA would deplete this peptide from CSF in an analogous manner to AD-associated reductions in CSF Aβ42. Additionally, total and phosphorylated tau protein levels were not significantly different from controls in CAA subjects, consistent with a lower level of tau-containing pathology in CAA. The combination of Aβ42 and total tau strongly discriminated cerebral amyloid angiopathy 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). These data suggest that Aβ40, Aβ42, and tau protein levels in the CSF may serve as sensitive biomarkers to identify patients with advanced CAA pathology.

Future Directions

There are many unanswered questions in CAA that represent potential important avenues of future research. We highlight some of the prominent areas below.

Mechanism of Small Vessel Injury

Microbleeds and white matter lesions appear to contribute to CAA-related brain injury as outlined above. There is also recent evidence to suggest that other MRI markers of cerebral small vessel disease may be important in CAA. These include ultrastructural damage detected by diffusion-tensor imaging[42,133] and small ischemic infarcts.[54,55] Untangling the

independent contributions of these lesions to CAA-related neurologic dysfunction could be an important step toward prevention.

Effect of Blood Pressure on Clinical Course

A recent subanalysis from the randomized-controlled trial PROGRESS suggests that blood pressure lowering may have an important effect in reducing recurrent ICH in general and CAA-related ICH in particular.[134] Although blood pressure appears not to be the primary causative agent in CAA, its impact on outcomes such as recurrent ICH, cognitive impairment, or progression of small vessel disease pathology remains to be determined.

Early Markers

Although the Boston criteria have been very useful in identifying patients with advanced CAA, these criteria are likely less specific in detecting individuals with early CAA. Furthermore, they remain indirect measures of the effects of Aβ-mediated pathology. Direct measures of vascular Aβ burden during life such as PiB-PET imaging or CSF Aβ may prove useful in identifying individuals in the early stages of the disease. Additionally, in vivo measures of abnormal vascular reactivity[41] may represent other tools to help distinguish individuals with nascent CAA pathology.

Prescribing Antithrombotic Therapy

Anticoagulation appears generally unsafe following CAA-related ICH, even for strong indications such as nonvalvular atrial fibrilation.[135] The relative risks and benefits are less clear for individuals with microbleeds only; a small case–control study suggested that these lesions may be an independent risk factor for warfarin-related ICH.[136] For the (presumably safer) alternative of antiplatelet therapy, there is also evidence to suggest increased ICH risk in CAA, particularly for individuals with larger numbers of microbleeds.[137,138] Larger, more definitive studies are required to settle these important questions, which could have considerable clinical implications.

Role of Antiamyloid Immunotherapy on Blood Vessels in CAA

The risks—and even possible benefits—of anti–β-amyloid therapy in individuals with CAA remain largely unknown. Animal studies have suggested that effective clearance of β-amyloid through immunotherapy may be possible.[139–141] Whether similar results are achievable in humans, and how they might affect future clinical impairment, remain to be determined.

Role and Clinical Impact of Cerebrovascular Aβ Deposition in Patients with Both AD and Advanced CAA

It remains uncertain whether advanced CAA can be definitively recognized in AD patients. Additionally, apart from its potentially important role in reaction to immunotherapy, the possibility that advanced CAA represents severe enough small vessel disease to modify the clinical, cognitive, or neuroimaging profile of AD needs to be clarified.

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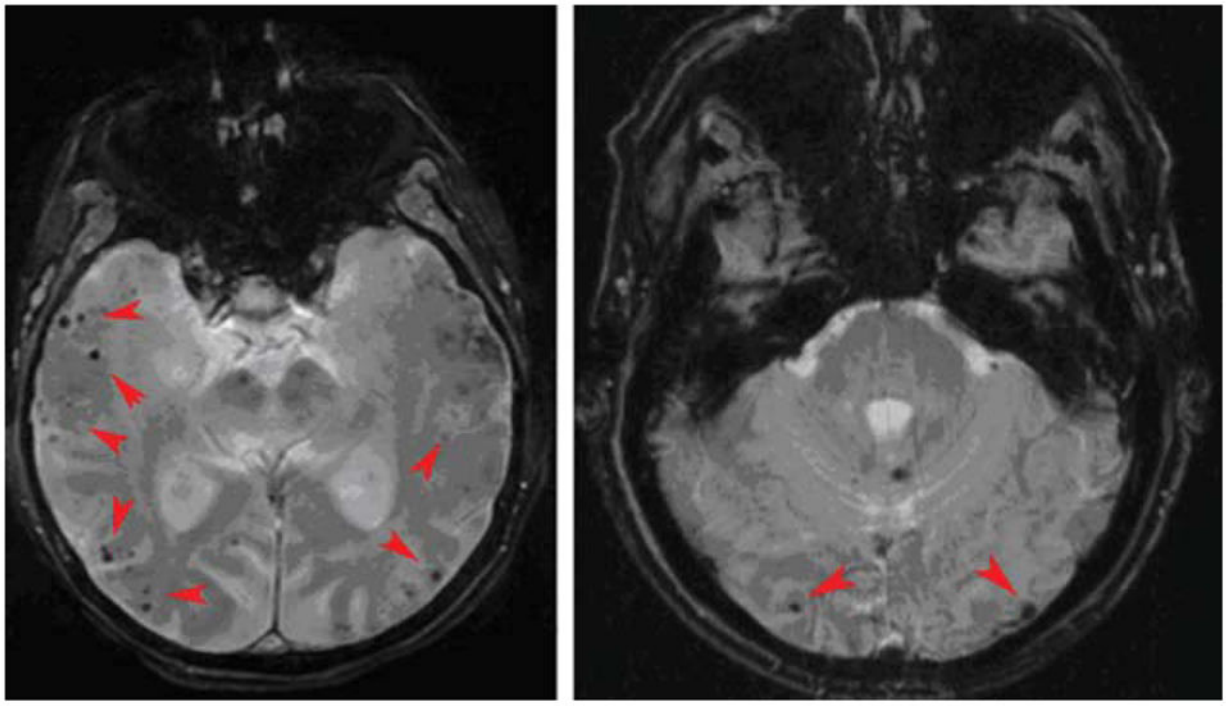

FIGURE 1.

Two examples of patients with probable cerebral amyloid angiopathy. Magnetic resonance imaging demonstrates multiple strictly lobar microbleeds *(red arrowheads)*.

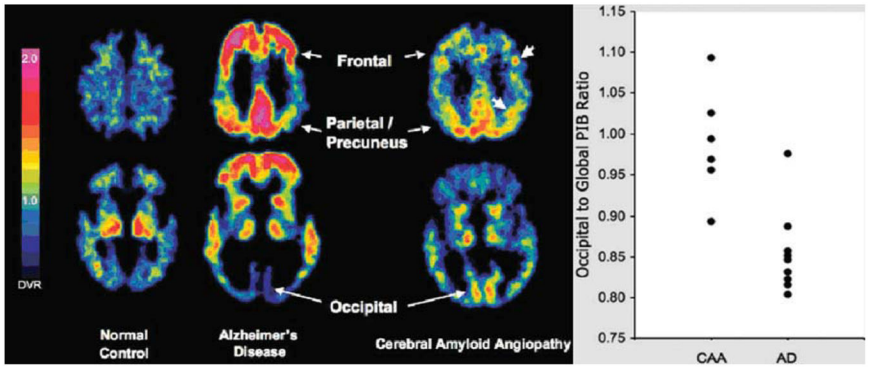

FIGURE 2.

Cerebral amyloid angiopathy (CAA) subjects show intermediate level of global Pittsburgh compound B (PiB) retention with occipital predominance. Representative PiB positron emission tomographic images at 2 transaxial levels from normal control (NC) (PiB-negative), Alzheimer disease (AD), and CAA (left panel). Compared with AD and NC, CAA subjects had an intermediate level of global PiB retention, but had relatively increased occipital retention compared with AD (right panel). Modified from Johnson et al.[121] DVR = distribution volume ratio.

TABLE 1

Comparison of Features of Cerebrovascular versus Parenchymal Senile Plaque Amyloid Deposition

Feature	Cerebrovascular Amyloid Deposition	Senile Plaque Amyloid Deposition
Predominant Aβ type	Aβ40	Aβ42 (particularly in diffuse plaques)
Location of Aβ deposition	Relative occipital lobe predominance	Frontal, parietal, temporal lobes
APOE allele risk factors	APOE ε4 (for amyloid deposition) and APOE ε2 (for vessel breakdown)	APOE ε4
Inflammatory subtype with reversible white matter hyperintensities	Occurs spontaneously as CAA-related inflammation	May occur iatrogenically as a result of amyloid immunotherapy or other candidate treatments targeting amyloid
Cerebral microbleeds	Lobar predominant, particularly occipital	Not associated with senile plaques
Location of white matter disease	Equal distribution between anterior and posterior subcortical regions (subgroup may have posterior-dominant white matter disease)	Equal distribution between anterior and posterior subcortical regions, but less extensive than advanced CAA

See text for more details discussion and details.

APOE = apolipoprotein E; CAA = cerebral amyloid angiopathy.

TABLE 2

Microbleeds in Alzheimer Disease

Study	Subjects	Prevalence	Predominant Location
Cordonnier et al 2006[93]	223	18%	Lobar
Pettersen et al 2008[96]	80	29%	Lobar
Hanyu et al 2003[94]	59	32%	Lobar
Atri et al 2005[92]	61	15%	Lobar
Nakata et al 2002[95]	38	18%	Lobar