

REVIEW ARTICLE**Emerging concepts in sporadic cerebral amyloid angiopathy****Andreas Charidimou,¹ Gregoire Boulouis,¹ M. Edip Gurol,¹ Cenk Ayata,^{2,3} Brian J. Bacskai,⁴ Matthew P. Frosch,^{4,5} Anand Viswanathan¹ and Steven M. Greenberg^{1,4}**

Sporadic cerebral amyloid angiopathy is a common, well-defined small vessel disease and a largely untreatable cause of intracerebral haemorrhage and contributor to age-related cognitive decline. The term ‘cerebral amyloid angiopathy’ now encompasses not only a specific cerebrovascular pathological finding, but also different clinical syndromes (both acute and progressive), brain parenchymal lesions seen on neuroimaging and a set of diagnostic criteria—the Boston criteria, which have resulted in increasingly detected disease during life. Over the past few years, it has become clear that, at the pathophysiological level, cerebral amyloid angiopathy appears to be in part a protein elimination failure angiopathy and that this dysfunction is a feed-forward process, which potentially leads to worsening vascular amyloid- β accumulation, activation of vascular injury pathways and impaired vascular physiology. From a clinical standpoint, cerebral amyloid angiopathy is characterized by individual focal lesions (microbleeds, cortical superficial siderosis, microinfarcts) and large-scale alterations (white matter hyperintensities, structural connectivity, cortical thickness), both cortical and subcortical. This review provides an interdisciplinary critical outlook on various emerging and changing concepts in the field, illustrating mechanisms associated with amyloid cerebrovascular pathology and neurological dysfunction.

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Abbreviations: CAA = cerebral amyloid angiopathy; ICH = intracerebral haemorrhage

Introduction

Cerebrovascular deposition of amyloid- β (also known as cerebral amyloid angiopathy, CAA) is a strikingly common finding in elderly people and a major cause of spontaneous intracerebral haemorrhage (ICH), as well as an important contributor to age-related cognitive decline (Viswanathan and Greenberg, 2011; Boulouis *et al.*, 2016). However, it is not a long time since CAA was considered a rather obscure pathological curiosity and innocent bystander in the elderly brain, often accompanying Alzheimer's disease. Despite the close molecular relationship between the two entities, CAA remains clinically distinct from Alzheimer disease, but has the potential to link cerebrovascular and neurodegenerative pathways in the ageing brain (Cordonnier and van der Flier, 2011). The CAA story is remarkable in that unlike most neurological disorders, the recognition of the underlying pathology preceded by many years the association with clinical syndromes and disease. In 1954, Stefanos Pantelakis from the University Psychiatric Clinic in Bel-Air, Switzerland, highlighted CAA as a distinct entity (Pantelakis, 1954). In his landmark paper, Pantelakis raised the hypothesis that vascular amyloid may originate in the brain (in line with modern concepts of amyloid pathophysiology) and—among other things—described what are still the pathological hallmarks of CAA: (i) preferential involvement of small arterioles and capillaries of the leptomeninges and cerebral cortex, without necessarily involving adjacent parenchymal; (ii) topographical distribution favouring posterior lobar brain regions (especially the occipital lobes); (iii) lack of involvement of white matter small vessels; (iv) association with increased age and dementia; (v) lack of association with hypertension and arteriosclerosis (the other main vessel disease, which preferentially affects the basal ganglia and brainstem); and (vi) lack of any link with systemic amyloidosis.

Since these early descriptions, understanding of the pathophysiological mechanisms and clinical imaging manifestations of CAA has increased substantially. CAA denotes not only a specific cerebrovascular pathological trait, but also a clinical syndrome (or syndromes), and a set of clinical imaging diagnostic criteria (the Boston criteria), which have resulted in increasingly detected disease during life (Linn *et al.*, 2010; Charidimou *et al.*, 2012a). Over the past decade we have also come to realise that the integrity of cerebral microvessels is critical for solute efflux from the interstitial fluid of the brain, as these molecules pass from brain into the perivascular drainage system and the systemic lymphatic circulation (Carare *et al.*, 2013). Cerebrovascular accumulation of amyloid can thus be viewed in some ways 'as a canary in a coal mine', an indicator of perivascular drainage failure (Carare *et al.*, 2013; Keable *et al.*, 2016). This process may set in motion a damaging disease process that both further exacerbates the clearance defects and triggers clinically relevant

haemorrhagic (Zhao *et al.*, 2015) and ischaemic brain injury (Reijmer *et al.*, 2016b).

This review update focuses on selected recent topics that have not been extensively covered in previous reviews and illustrate emerging and changing concepts in sporadic CAA, including the neurological effects and underlying biology of the disease. Given the fast-moving CAA research landscape (Charidimou *et al.*, 2016a) in the current paper we are not covering all the clinical and imaging aspects of CAA in detail, given the more specific published reviews (Greenberg *et al.*, 2009b, 2014; Pantoni, 2010; Smith *et al.*, 2012b; Reijmer *et al.*, 2016b). Instead, emphasis is given to concepts, findings and theoretical frameworks of the disease, with examples from the literature to illustrate these points. Finally, our paper focusses on the more common sporadic CAA—for the rare genetic forms of cerebrovascular amyloid accumulation and CAA-related inflammation, please see other reviews and recent publications for further information (Revesz *et al.*, 2009; Charidimou *et al.*, 2012a; Auriel *et al.*, 2016).

Cerebral amyloid angiopathy clinical aspects

Pathologically-defined CAA is common in the elderly and advancing age is the strongest known risk factor for sporadic CAA (Vinters, 1987). Population-based autopsy studies indicate a CAA prevalence of 20–40% in nondemented, and 50–60% in demented elderly populations (age range for both groups 80–90 years) (Keage *et al.*, 2009). For severe CAA, prevalence in demented and nondemented elderly groups is 30–40% and 7–24%, respectively (Keage *et al.*, 2009). In Alzheimer's disease brains, CAA is identified in an estimated 85–95% of the cases when sought diligently (Kalaria and Ballard, 1999; Jellinger, 2002). Only a relatively small proportion of these older individuals are diagnosed during life with CAA-related clinical symptomatology (acute or progressive). The sentinel clinical presentations of CAA include spontaneous lobar ICH, cognitive impairment and dementia (either post ICH or in patients without stroke) and transient focal neurological episodes ('amyloid spells') often associated with acute convexity subarachnoid haemorrhage or cortical superficial siderosis. The relative frequency of the different CAA clinical presentations is hard to assess, as it is heavily dependent on making an accurate diagnosis of underlying CAA in different settings using appropriate MRI sequences (including blood sensitive sequences). The association of these presentations with objective assessments of clinical frailty, comorbidities or chronological age *per se* are under investigation. The key neuroimaging signatures of the disease on clinical MRI include multiple strictly lobar cerebral microbleeds, cortical superficial siderosis, white matter hyperintensities, cortical microinfarcts and MRI-visible perivascular spaces in the

centrum semiovale (Greenberg *et al.*, 2014). An overview of the key CAA clinical presentations and the significance/role of different MRI markers of small vessel disease in each of these based on the totality of current evidence is provided in Table 1.

Dementia and cognitive impairment in cerebral amyloid angiopathy

Cognitive impairment in CAA was first reported over two decades ago (Gray *et al.*, 1985; Greenberg *et al.*, 1993). Dissecting the independent impact of CAA on cognition,

however, is confounded by co-existing Alzheimer's disease and other age-related pathologies (e.g. sporadic non-amyloid microangiopathy). Recent studies in older community dwelling persons have suggested an association between moderate-to-severe CAA pathology and lower perceptual speed and episodic memory (Arvanitakis *et al.*, 2011). In these cohorts, CAA is a common finding and appears to independently contribute to the level of cognitive deficit beyond Alzheimer's disease or other accompanying pathologies (Pfeifer *et al.*, 2002; Boyle *et al.*, 2015). In one community-based cohort, individuals harbouring CAA not only had increased risk of dementia [odds ratio (OR): 1.237;

Table 1 Overview of the sentinel clinical presentations of CAA and the role of key MRI small vessel disease biomarkers and imaging signatures of the disease within each of these

CAA/SVD MRI biomarkers	Sentinel clinical presentations of CAA			
	Spontaneous lobar ICH	Post-ICH dementia	TFNEs ('amyloid spells')	MCI/dementia (without ICH)
Lobar CMBs	+++	+++	++	++
	Diagnosis (Boston criteria)	Diagnosis (Boston criteria)	Diagnosis (Boston criteria)	Diagnosis (Boston criteria)
	Clinical function	Severity/progression		Clinical function?
	Severity/progression	Prognosis: new dementia		Severity/progression?
	Prognosis: rICH risk			Prognosis?
CSS	++	++	+++	–Significance?
	Diagnosis (Boston criteria)	Clinical function?	Diagnosis (Boston criteria)	
	Severity/progression	Prognosis: new onset dementia	Clinical function	
	Prognosis: rICH risk		Severity/progression	
Acute cSAH	–	–	+++	–
			Diagnosis (Boston criteria)	
			Clinical function	
			Severity/progression	
			Prognosis?	
WMH	+++	+++	+	++
	Severity/progression	Clinical function?	Significance?	Clinical function
		Severity/progression		Severity/progression
CSO-EPVS	+++	++	++	++
	Diagnosis	Clinical relevance?	Diagnosis (Revised criteria?)	Significance?
	Significance?			
Small DWI lesions	+++	?	++	+
	Severity/progression?		Clinical function?	Prognosis?
	Prognosis?		Severity/progression?	
			Prognosis?	
Cortical microinfarcts	?	?	?	+++
				Clinical function?
				Severity/progression?
				Prognosis?

+ / – denotes the relative frequency or absence and overall significance of each of the markers, respectively. The clinical role of MRI biomarkers was considered in the following areas: diagnosis, clinical function, severity/progression of CAA and clinical prognosis.

+ = low; ++ = moderate; +++ = high frequency; – = rare; ? = unknown role; CMB = cerebral microbleed; cSAH = cortical subarachnoid haemorrhage; CSO-EPVS = centrum semiovale-enlarged periventricular space; DWI = diffusion weighted imaging; rICH = recurrent ICH; TFNEs = transient focal neurological episodes; WMH = white matter hyperintensity.

Ratings represent the authors' overall consensus based on the literature cited in the corresponding sections of the text and clinical practice.

95% confidence interval (CI): 1.082–1.414] but a faster rate of decline in both global and domain-specific cognition (Boyle *et al.*, 2015).

In a hospital-based setting, patients with CAA without dementia evaluated for stroke or stroke-like symptoms appeared to be at high risk for developing dementia (Moulin *et al.*, 2016). Interestingly, in this study, the history of previous CAA-related ICH was not associated with the degree of cognitive deficits. Indeed previous work has suggested that cognitive decline in CAA may precede ICH (Viswanathan *et al.*, 2008; Cordonnier *et al.*, 2010; Xiong *et al.*, 2016b), thus indicating that CAA-related cognitive decline may occur independently of symptomatic ICH. In another hospital-based study, patients with CAA without dementia evaluated for stroke or stroke-like symptoms appeared to perform significantly worse on nearly all tests in a standard neurocognitive battery compared to a group of healthy controls with similar age and education level (Xiong *et al.*, 2016a). In this study, these deficits were clearly present even though the majority of patients did not have self-reported cognitive concerns or cognitive deficits (Xiong *et al.*, 2016a). In the analyses of the relationship between these cognitive deficits and neuroimaging biomarkers, lower total brain volume was associated with slower processing speed and worse executive function, and white matter hyperintensity volume was related to executive function in CAA patients (Xiong *et al.*, 2016a).

Despite the clinical observation of cognitive impairment in CAA, the frequency, severity, and specific cognitive profile of CAA patients are not well understood (Schrag and Kirshner, 2016). To address this question, a pilot study reported neuropsychological and neuroimaging data from an ongoing prospective cohort (Functional Assessment of Vascular Reactivity in CAA) (Case *et al.*, 2016). This study compared the neuropsychological test results in non-demented CAA participants ($n = 34$) to participants with dementia caused by Alzheimer's disease ($n = 16$), mild cognitive impairment ($n = 69$), and ischaemic stroke ($n = 27$) (matched for stroke severity to CAA participants). The mean test scores for CAA patients were significantly lower than norms for memory, executive function, and processing speed. A large proportion of these CAA patients (79%) fulfilled criteria for mild cognitive impairment based on low cognitive performance and cognitive concerns. Compared to Alzheimer's disease, CAA patients had similarly low executive function scores, but relatively preserved memory. CAA participants' scores were lower than those of the ischaemic stroke group for executive function and processing speed. Lower processing speed scores in CAA were associated with higher white matter hyperintensity volumes (Case *et al.*, 2016).

Taken together, current evidence suggests that mild cognitive impairment and dementia are very prevalent in clinically diagnosed CAA patients. The overall cognitive profile of CAA is more similar to that seen in classic vascular cognitive impairment than Alzheimer's disease (i.e.

executive dysfunction and impaired processing speed with relatively preserved episodic memory). White matter ischaemic lesions may underlie some of the impaired processing speed seen in CAA. CAA-related dementia and vascular cognitive impairment are likely the result of both small, spatially distributed brain injuries including cerebral microbleeds (Moulin *et al.*, 2016), cortical microinfarcts, and altered structural connectivity. In support of this hypothesis, a recent study examining brain networks in CAA as a surrogate measure of global small-vessel pathology showed that lower global network efficiency was independently related to worse performance on tests of processing speed and executive functioning (Reijmer *et al.*, 2015).

Clinical imaging expression and spectrum of cerebral amyloid angiopathy

CAA is most often recognized in life by symptomatic, spontaneous ICH, preferentially affecting cortical-subcortical (lobar) regions (especially the occipital and posterior temporal lobes) (Rosand *et al.*, 2005). These individuals have predominantly severe CAA (Alonzo *et al.*, 1998), with small burden of neurofibrillary tangles and senile plaques on neuropathology (Charidimou *et al.*, 2015c). Multiple recurrent CAA-related haematomas can occur over months or years (at a rate of recurrence on the order of 10% per year) (Biffi *et al.*, 2010), with progressive neurological decline. CAA may also be an important risk factor or cause for ICH related to oral anticoagulation use and thrombolysis-related haematomas in acute ischaemic stroke (Charidimou *et al.*, 2015d; Mattila *et al.*, 2015). Reliable assessment of an individual's haemorrhagic burden over time and prevention of future ICH is thus a key component in the clinical management of CAA patients (see below).

In this context, characterization of the expanding clinical imaging spectrum of CAA has been refined substantially in the past years with the broader availability of brain MRI (Boulouis *et al.*, 2016). In addition to lobar ICH, other characteristic MRI biomarkers of CAA now include strictly lobar microbleeds, cortical superficial siderosis, white matter hyperintensities (especially posterior-predominant), MRI-visible perivascular spaces in the cerebral white matter and cortical microinfarcts (Fig. 1). These neuroimaging markers probably reflect related but distinct aspects of CAA pathophysiology (Charidimou and Jager, 2014). An important advance in the field has been the recent publication of international consensus standards for describing and reporting many of these small vessel disease lesion types (Wardlaw *et al.*, 2013). Multiple strictly lobar microbleeds detected on T_2^* /SWI (susceptibility-weighted imaging) MRI are accepted as one of the hallmark biomarkers for CAA presence and are useful for CAA diagnosis within the Boston criteria (Knudsen *et al.*,

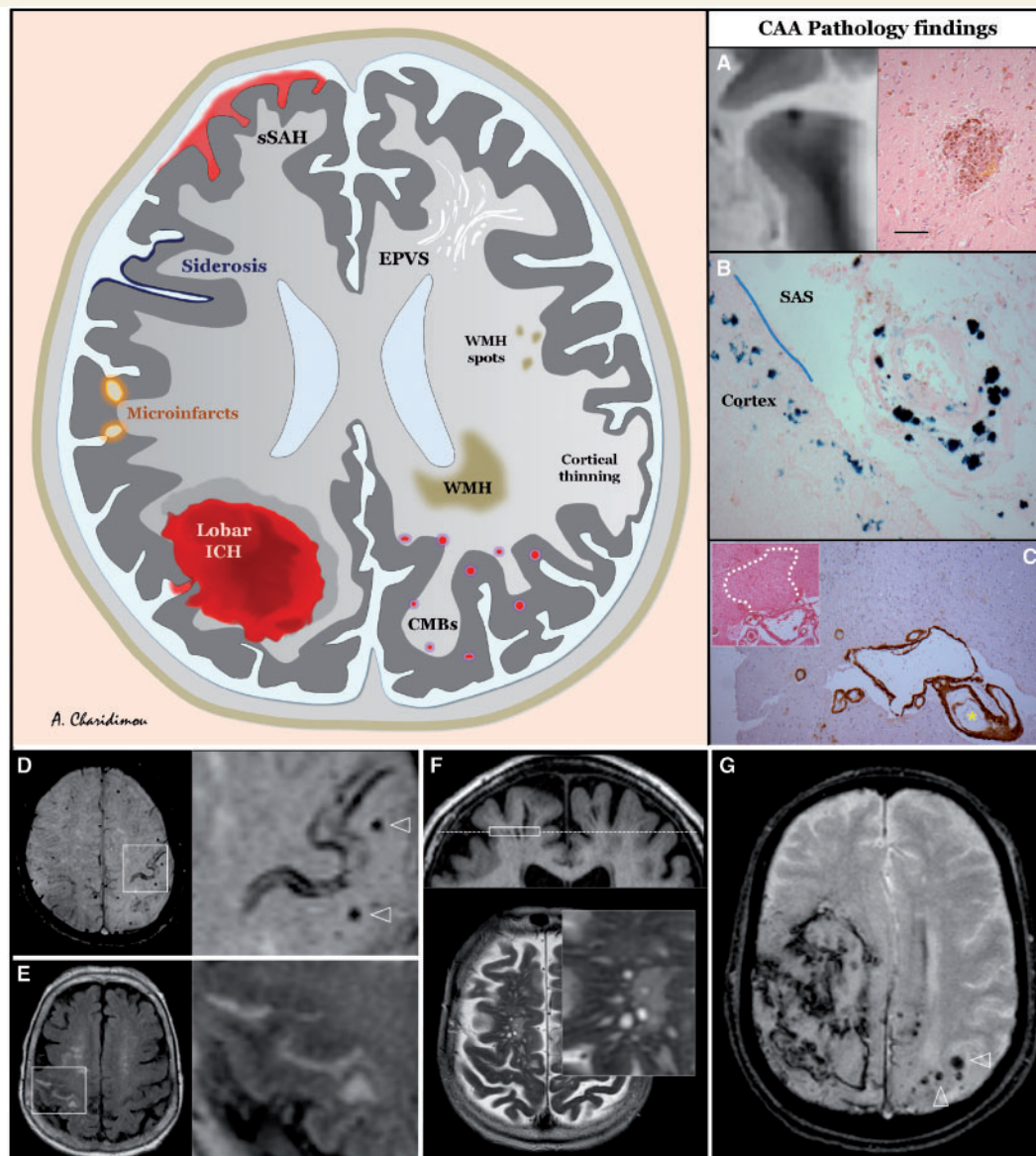


Figure 1 Schematic representation of the spectrum of haemorrhagic and ischaemic manifestations of sporadic CAA, visible on structural MRI, including three key common neuropathological lesions seen in CAA brains. (A) A lobar cerebral microbleed identified on post-mortem 7 T MRI in the brain tissue of an 81-year-old male with dementia and severe CAA on pathology. On haematoxylin and eosin stain, brown and yellow deposits representing haemosiderin, and haematoidin, are seen, indicating that this haemorrhage is not chronic but subacute. (B)

Prussian blue stain from an area corresponding to cortical superficial siderosis on *in vivo* MRI of a patient with advanced CAA. Blue deposits corresponding to haemosiderin are seen in the subarachnoid space (SAS) surrounding a leptomeningeal arteriole (which shows a vessel-within-vessel appearance) and in the superficial layers of the cortex. (C) A cortical microinfarct identified on histopathological examination. Note the severe vascular amyloid deposition (dark brown: immunostained for amyloid- β) in both the overlying leptomeningeal small vessels of different diameters and two cortical arterioles in the vicinity of the microinfarct. *Bottom*: Imaging CAA in clinical practice. 1.5 T brain MRI sequences. (D) Seventy-five-year-old male; initial evaluation of stereotyped episodes of right sided of tingling in the past year; axial section of SWI demonstrating a focus of cortical superficial siderosis on both banks of the left central sulcus, and multiple strictly lobar microbleeds (arrowheads in magnification).

(E) Eighty-eight-year-old female with history of cognitive complaints, 6 months after initial imaging demonstrating multiple lobar microbleeds. Persistent headache and recent episode of left hand numbness and weakness; axial section of FLAIR sequence showing a linear hyperintensity in the right central sulcus, corresponding to acute subarachnoid blood. (F) Seventy-seven-year-old male otherwise meeting Boston criteria for CAA; coronal section (*top*) of T₁-weighted, and axial section of T₂-weighted sequences showing multiple dilated perivascular spaces (magnification) in the centrum semiovale, following the path of small calibre arteries. Diffuse widening of cerebral sulci due to marked cortical atrophy can also be appreciated. (G) Sixty-five-year-old male with acute onset of right hemiplegia and impaired consciousness at hospital arrival. Large right lobar (mostly parietal) ICH ruptured into the convexities and subarachnoid space. Contralateral multiple strictly lobar microbleeds are seen. EPVS = enlarged perivascular space; CMBs = cerebral microbleeds; sSAH = spinal subarachnoid haemorrhage; WMH = white matter hyperintensity.

2001; Linn *et al.*, 2010) and to assess disease evolution (Pasquini *et al.*, 2016). Strictly lobar cerebral microbleeds within these criteria have a high positive predictive value for CAA even in individuals without ICH presentations in a hospital-based setting (specificity >90% and positive predictive value >87%) (Martinez-Ramirez *et al.*, 2015). This is of particular clinical relevance, as CAA is increasingly recognized to present without major haemorrhage. Lobar microbleeds also frequently occur among presumably healthy people as a result of previously clinically silent CAA (Mesker *et al.*, 2011), but also in the absence of CAA, yielding low overall specificity in this setting (Martinez-Ramirez *et al.*, 2015). However, the detection of cerebral microbleeds in different clinical settings raises thorny clinical dilemmas regarding their biological significance and how they might affect treatment decisions, especially regarding antithrombotic drug use (Greenberg *et al.*, 2009b; Wang *et al.*, 2014). Clinical radiological criteria for CAA-related inflammation have also been validated (Auriel *et al.*, 2016), allowing non-invasive diagnosis of this potentially treatable meningoencephalitis syndrome (Eng *et al.*, 2004).

Recent data have implicated acute or chronic haemorrhage within or adjacent to the cortical sulci (often described as cortical superficial siderosis when chronic or as sulcal subarachnoid haemorrhage when acute) as key haemorrhagic neuroimaging signatures of CAA (Charidimou *et al.*, 2015b). They likely reflect repeated episodes of blood leaking into the subarachnoid space from brittle and fragile CAA affected vessels. Siderosis is emerging as perhaps the most clinically relevant manifestation of the disease: (i) it is a trigger of transient focal neurological symptoms ('amyloid spells') (Greenberg *et al.*, 1993; Charidimou *et al.*, 2012b), expanding the CAA clinical imaging spectrum (Raposo *et al.*, 2011; Calviere *et al.*, 2016); (ii) it has been shown to carry a very high risk of future symptomatic lobar ICH (Linn *et al.*, 2010; Charidimou *et al.*, 2013c) with important implications for CAA clinical care, such as strict blood pressure control (Gorelick *et al.*, 2011; Biffi *et al.*, 2015; Hemphill *et al.*, 2015; Carcel *et al.*, 2016) and avoiding antithrombotics unless otherwise strongly indicated (Biffi *et al.*, 2010; Charidimou *et al.*, 2012a); and (iii) it may be an independent risk factor for new onset dementia after ICH (Moulin *et al.*, 2016). Of note, siderosis exerts these effects independent of, and above any effect of coincident microbleeds (Greenberg *et al.*, 2004; Biffi *et al.*, 2010). Recently, consensus standards for rating and reporting cortical superficial siderosis have been suggested and are encouraged for use in observational and clinical studies (Charidimou *et al.*, 2015b). The emerging key role of cortical superficial siderosis in neurological dysfunction in CAA might be linked with the neuropathological observation of more severe leptomeningeal CAA compared to parenchymal and between superficial and deep cortical layers in any given brain (Kovari *et al.*, 2013).

Role of molecular imaging in cerebral amyloid angiopathy

While CAA appears detectable by molecular amyloid imaging (Klunk *et al.*, 2004; Bacskai *et al.*, 2007; Greenberg *et al.*, 2008) the clinical diagnostic utility of amyloid PET in suspected CAA remains undefined. Non-demented patients with CAA show higher global Pittsburgh compound B (PiB)-PET retention when compared to healthy control subjects and higher occipital-to-global PiB ratios compared to patients with Alzheimer's disease (Johnson *et al.*, 2007; Ly *et al.*, 2010). However, due to the frequent occurrence of high PiB-PET uptake in the healthy elderly likely reflecting incipient Alzheimer disease, specificity is limited; one study reported sensitivity of 91%, and specificity of 55% compared to healthy controls (Baron *et al.*, 2014). A negative PiB scan appears to rule out severe CAA and may in the future have clinical research implications for prognostication, treatment decisions, and patient selection for drug trials. A small study recently tested the clinical relevance of florbetapir-PET, another amyloid tracer, in distinguishing CAA-related lobar ICH from hypertensive ICH (Gurol *et al.*, 2016). In a study sample of cognitively normal patients, including 10 lobar haemorrhages with a clinical imaging diagnosis of probable CAA and nine with deep haemorrhages and without evidence for CAA of similar age (66.9 versus 67.1 years), sex, and leukoaraiosis volumes, the mean global cortical florbetapir uptake was higher in CAA versus non-CAA ($P = 0.001$). Based on visual rating for positive/negative florbetapir, all 10 patients with CAA versus 1/9 non-CAA patients were classified as positive (sensitivity: 100%; 95% CI: 66%–100% and specificity: 89%; 95% CI: 51–99% for determination of probable CAA) (Gurol *et al.*, 2016). The general conclusion is similar to previous studies using PiB-PET: a negative scan almost certainly rules out probable CAA—at least in these specific and well-defined comparison groups used in the study, 'probable' CAA with haemorrhage and deep hypertensive-related haemorrhage.

The clinical usefulness of amyloid-PET for CAA diagnosis in everyday practise currently remains limited and under investigation. Further larger prospective studies are needed to provide external validation, and test whether amyloid-PET can be useful for detecting CAA pathology in cases where the diagnosis is uncertain. Examples would include cases with mixed location of ICH (both lobar and deep), single lobar haemorrhage without microbleeds (labelled as 'possible' CAA) as well as cases with microbleeds or cortical superficial siderosis without any haematomas. A large prospective study of such uncertain cases with long follow-up is required to determine the sensitivity and specificity of amyloid imaging in these settings and at earlier stages of suspected CAA. Development of a molecular imaging tracer specific for vascular amyloid would be a major step forward for the field and preclinical studies continue to explore possible candidates (Jia *et al.*, 2014, 2015). Other

novel methods, such as early-phase PiB-PET (Farid *et al.*, 2015) and tau imaging, might help test similarities and differences between CAA and Alzheimer's disease in living individuals (Villemagne *et al.*, 2015), although given the strong overlap between these pathologies, it is unlikely that any technique in isolation will fully distinguish these two entities.

Amyloid imaging has recently become an important tool in CAA research to explore mechanisms and test spatial and quantitative correlations between proposed CAA-related brain lesions and the inciting pathology (i.e. vascular amyloid). In a cross-sectional study, higher PiB retention was detected at the sites (i.e. shells concentrically surrounding the bleeds) of lobar microbleeds in CAA when compared to other locations with high-probability to show CAA-related microbleeds (Dierksen *et al.*, 2010). Using a similar approach, in a longitudinal analysis of follow-up MRIs (median of 19 months after baseline), sites of future microbleeds demonstrated increased PiB retention relative to simulated lesions placed according to a probability density map (distribution volume ratio 1.34 versus 1.14, $P < 0.0001$) with fall-off at increasing distances from sites of future microbleeding (Gurol *et al.*, 2012). Despite the limitations imposed by the relatively poor spatial resolution of amyloid-PET, resulting in some imprecision for co-localizing PiB retention and haemorrhage location, these studies provide some proof of the concept that vascular amyloid deposition might be a key contributor to lobar microbleeds and macrobleeds. However, the exact mechanisms for these associations remain uncertain. Also, another study showed a positive correlation between leukoaraiosis volume and global PiB retention in patients with CAA but not in healthy controls or patients with Alzheimer's disease, suggesting that predominantly vascular amyloid deposition rather than parenchymal might drive this association (Gurol *et al.*, 2013). More recently, a study suggested that MRI-visible high degree centrum semiovale perivascular spaces, a novel CAA-related MRI marker, were correlated with a higher median amyloid PiB retention across a wide range of cerebrovascular amyloid deposition, after adjusting for age, microbleeds and white matter hyperintensities (Charidimou *et al.*, 2015a).

Cerebral amyloid angiopathy: the search for clinical trials surrogate markers

Although conventional CAA neuroimaging biomarkers are currently used for diagnosis and clinical monitoring, none has yet emerged as a valid clinical trials surrogate marker (Greenberg *et al.*, 2014). This apparent paradox might be partly due to the fact that these haemorrhagic and non-haemorrhagic structural focal lesions used clinically are only the tip of the iceberg and fail to capture the

cumulative large-scale impact of the disease. Also, the MRI-histopathological basis of small vessel disease neuroimaging biomarkers still needs to be defined, representing a remarkable lacuna in the field (Gouw *et al.*, 2011). For example, lesion-by-lesion analysis has been reported for fewer than 100 microbleeds (Fazekas *et al.*, 1999; Tatsumi *et al.*, 2008; Schrag *et al.*, 2010) often using relatively insensitive T_2^* -weighted techniques. Of note, the large numbers of cerebral microbleeds noted by MRI are rarely seen in autopsy brain specimens, a disconnect that likely reflects the ability of T_2^* -weighted MRI to fully sample the brain to an extent not achievable by histology. Although microbleeds are strongly associated with advanced CAA and it is commonly assumed that amyloid deposition in the walls of cortical vessels directly causes microbleeding, a recent detailed *ex vivo* 7 T MRI study challenged this notion. In 7/19 identified microbleeds, the presumed involved vessel could be identified on histopathological sectioning. Only one of these vessels was positive for amyloid- β at the site of rupture. Moreover, the density of amyloid- β positive cortical vessels was lower in areas surrounding microbleeds, compared to control areas (van Veluw *et al.*, 2017). Extremely limited data exist for perivascular spaces and siderosis. Brain banks (comprised of large brain donation programmes and collaborative initiatives) will be essential, in combination with new research techniques, in validating biomarkers in the field (Samarasekera *et al.*, 2013; McAleese *et al.*, 2016; Skrobot *et al.*, 2016).

For CAA-related cognitive impairment, a major reason that no single neuroimaging surrogate marker has emerged is the mismatch between the lesion types that are most MRI detectable versus those that are actually numerous enough to substantially damage brain connections and mediate cognitive dysfunction. Cerebral microbleeds or lacunes of presumed vascular origin (Wardlaw *et al.*, 2013) for example, are readily visualized by MRI, but their total burden is typically only one to two per brain (Longstreth *et al.*, 1998; Vernooij *et al.*, 2007, 2008) in community dwelling elderly, and <10 – 20 even in brains with advanced small vessel disease (Greenberg *et al.*, 2004; Viswanathan *et al.*, 2006a; Herve *et al.*, 2009). Cerebral microinfarcts hypothesized to play a key role in vascular cognitive impairment (Smith *et al.*, 2012b), conversely, are estimated to number in the hundreds or thousands per CAA brain (Westover *et al.*, 2013; Auriel *et al.*, 2015), but at mean diameter of $\sim 200 \mu\text{m}$ (Okamoto *et al.*, 2009; Smith *et al.*, 2012a; Westover *et al.*, 2013), are largely invisible to conventional MRI.

Finally, haemorrhagic and non-haemorrhagic structural lesions discussed seem to represent vascular-mediated injury to the brain rather than abnormalities of the vessels themselves. Thus, they probably measure late and irreversible steps in the postulated pathways leading from vascular dysfunction to brain injury and clinical dysfunction.

Neuropathological aspects of cerebral amyloid angiopathy and differences with ‘hypertensive arteriopathy’

CAA results from a chronic degenerative process by which the media of parenchymal arterioles undergoes progressive loss of its smooth muscle cells with simultaneous accumulation of an eosinophilic hyaline material (Attems *et al.*, 2011), mostly composed of the more soluble, amyloid- β_{40} species. This is in contrast to amyloid plaques found in Alzheimer’s disease, predominantly composed of amyloid- β_{42} species. The vessels affected by amyloid- β can show secondary vasculopathic changes, including fibrinoid necrosis, loss of smooth muscle cells, wall thickening, microaneurysm formation, and perivascular blood breakdown products deposition (Love *et al.*, 2014). A specific and important subtype of CAA is capillary CAA, which has received lots of attention recently (Attems *et al.*, 2011). This forms the basis for the CAA classification into two pathological types: CAA type 1, characterized by amyloid in cortical capillaries (with or without involvement of other vessels), and CAA type 2, where amyloid deposits are restricted to leptomeningeal and cortical arteries, but not capillaries (Attems *et al.*, 2011). Recently, the neuropathological and clinical characteristics of capillary CAA were investigated for the first time in a subset ($n = 300$; aged ≥ 85 years) of the Vantaa 85 prospective population-based study (Makela *et al.*, 2015). The authors reported that capillary CAA was most frequent in the occipital lobe, while CAA type 1 was associated with the severity of CAA overall ($P < 0.001$), dementia ($P < 0.001$), severe Alzheimer’s-type neuropathology (P -value 0.09 for CERAD C and 0.017 for Braak stages V–VI), and APOE $\epsilon 4$ (but not $\epsilon 2$) allele carrier status ($P < 0.001$) (Makela *et al.*, 2015). Immunohistochemical analysis in one study revealed that capillary CAA is associated with altered expression of sphingolipids, likely reflecting inflammatory pathways involvement (de Wit *et al.*, 2016).

When CAA is noted in the subarachnoid space, the amyloid deposits are usually adventitial rather than medial in the walls of larger affected arterioles in a chunky, spiral-like fashion, suggesting they may have resulted from aggregates of amyloid- β that came to lodge in arterial adventitia through the perivascular drainage system (Vinters, 2015). The distribution of CAA pathology shows a characteristic patchy pattern (Vinters, 1987), whereby foci of vessels severely affected by CAA may be adjacent to other vessel segments with mild or absent amyloid- β deposition (Vinters, 1987; Attems *et al.*, 2011), contributing to the heterogeneity of the disease. The severity and extent of histological changes provide the basis of several CAA neuropathological scoring systems (Vonsattel *et al.*, 1991b; Olichney *et al.*, 1995; Thal *et al.*, 2003), each with strengths and limitations (Attems, 2005; Attems

et al., 2011). Recently, a standardized consensus neuropathological protocol for rating CAA was developed (Love *et al.*, 2014), potentially allowing comparison of pathological data across centres.

In contrast to CAA, which is relatively easy to define, the other common subtype of age-related small vessel disease remains less clearly defined at a diagnostic or molecular level and is broadly described as ‘hypertensive arteriopathy’ (Pantoni, 2010). The umbrella term ‘hypertensive arteriopathy’ groups together a spectrum of sporadic non-amyloid small vessel disease pathologies often associated with advanced age (but not clearly age-driven), hypertension (though the disease is not necessarily, or even often, related specifically to hypertension), diabetes mellitus, and other common vascular risk factors (Pantoni, 2010). Hypertensive arteriopathy is characterized pathologically by collagenous thickening of the vessel wall with narrowing of the lumen and progressive loss of smooth muscle, and sometimes by exudation of fibrin and other serum proteins or by scanty mural deposition of lipid (Pantoni, 2010). Different pathological subtypes include arteriolosclerosis, fibrinoid necrosis, and lipohyalinosis (Pantoni, 2010; Charidimou *et al.*, 2016b). The term ‘sporadic non-amyloid microangiopathy’ has been recently suggested as a more accurate alternative to group together these diseases (Charidimou *et al.*, 2016b).

Despite the limitations in definitions and the lack of widely accepted terms for this small vessel pathology, the rationale for making a clear distinction between CAA and sporadic non-amyloid microangiopathy is 2-fold. First, the two pathological processes are predominantly found in small vessels of different brain areas. In contrast to CAA, which typically affects the small arteries and arterioles in the cerebral cortex and overlying leptomeninges, sporadic non-amyloid microangiopathy predominantly affects the small perforating end arteries of the deep grey nuclei and deep white matter (Pantoni, 2010; Charidimou *et al.*, 2016b). In parallel with this distribution of the underlying pathology, sporadic non-amyloid microangiopathy is commonly associated with cerebral microbleeds and spontaneous ICH in deep brain regions (e.g. basal ganglia, thalamus, and brainstem), whereas CAA is characterized by cerebral microbleeds and spontaneous ICH in a lobar distribution (cortical–subcortical), as well as cortical superficial siderosis. This allows for the clinical distinction of the two disorders based on the Boston diagnostic criteria (Knudsen *et al.*, 2001; Smith and Greenberg, 2003; Linn *et al.*, 2010; Martinez-Ramirez *et al.*, 2015). The key neuropathological, clinical and imaging differences of CAA versus sporadic non-amyloid microangiopathy are summarized in Table 2. Of major clinical relevance, the two small vessel diseases have a different natural history and inherently distinct recurrent haemorrhagic risk in patients presenting with ICH: CAA-related lobar ICH carries a significantly higher risk for recurrence compared to deep ICH related to sporadic non-amyloid microangiopathy (Hill *et al.*, 2000; Bailey *et al.*, 2001; Viswanathan *et al.*, 2006b; Weimar *et al.*, 2011). This is particularly relevant for treatment decisions, especially antithrombotic use in the setting of

small vessel disease (see ‘Therapeutic aspects’ section). Subdividing cerebral small vessel disease into CAA and non-CAA components may be an oversimplification as patients often have a mix of both pathologies. However, this distinction serves to distinguish the differences in the putative pathophysiology and different clinical and pathological consequences of the two diseases (Table 2).

Emerging concepts in cerebral amyloid angiopathy pathophysiology

Perivascular drainage, vascular pathophysiology and cerebral amyloid angiopathy-related brain injury

The pathogenesis of CAA and its downstream effects on the brain are incompletely understood and highly complex. However, there is little evidence that age-associated

cerebrovascular accumulation in sporadic CAA is driven by amyloid- β overproduction. Instead, current evidence suggests that amyloid- β accumulation is driven largely by reduced peptide clearance (Deane *et al.*, 2009; Mawuenyega *et al.*, 2010). The small vessels of the brain appear to play a major role in this clearance process, both as sites of efflux across the blood–brain barrier (Zlokovic *et al.*, 2010) and as the site of intramural perivascular drainage of amyloid- β from the brain interstitial fluid (Weller *et al.*, 1998; Marin-Padilla and Knopman, 2011). Hence, the view of CAA as a protein elimination failure angiopathy has been devised (Carare *et al.*, 2013; Carare and Kalara, 2016) and provides the most conceptually compelling model to explain this failure and the pathophysiological basis of disease progression.

Details on the ‘garbage truck of the brain’, including brain pathways for lymphatic drainage and for the convective influx/lymphatic communication pathways are the focus of intensive scrutiny and not definitively established (Nedergaard, 2013; Tarasoff-Conway *et al.*, 2015). However, the prevailing model of perivascular (peri-arterial) drainage of interstitial fluid relies on vessel pulsations

Table 2 Key neuropathological, clinical and neuroimaging characteristics of the two major sporadic cerebral small vessel diseases: CAA and ‘hypertensive arteriopathy’

Characteristics	CAA	Sporadic non-amyloid microangiopathy (‘hypertensive arteriopathy’)
Small vessel pathology	Amyloid- β deposition and associated vasculopathy in cortical and leptomeningeal vessels.	A range of different features, e.g. arteriolosclerosis, fibrinoid necrosis, mural damage etc.
Risk factors	Age, APOE e4 and e2.	Age, hypertension, diabetes, smoking.
Associated clinical syndromes		
ICH	Lobar (cortical-subcortical), cerebellar?	Typically deep: basal ganglia, thalamus, pons cerebellum; sometimes lobar.
	Associated with high risk of recurrence (7–12% per year).	
Ischaemic stroke	Not typically associated with lacunes.	Lacunar syndromes.
	Uncertain role other than affecting treatment decisions, e.g. antithrombotic drugs, thrombolysis etc.	
Other clinical syndromes	Transient focal neurological episodes (‘amyloid spells’), cognitive impairment and dementia, inflammatory CAA.	Vascular cognitive impairment and dementia.
MRI markers of small vessel disease		
CMBs	Strictly lobar.	Predominantly deep, with or without lobar.
cSS	Very common: ~40% in symptomatic CAA.	Rare: <5% of deep ICH.
MRI-visible perivascular spaces	Centrum semiovale (i.e. cerebral white matter).	Basal ganglia.
White matter hyperintensities	Posterior predominance, white matter spots.	No predilection for brain region, peribasal ganglia.
Lacunes	Not typically present, more superficial in the cerebral white matter.	Common, usually in the basal ganglia or deep white matter.
Diagnosis	Boston criteria, based on the presence of multiple strictly lobar CMBs or macrobleeds and cSS.	No established criteria available; diagnosed in patients not fulfilling Boston criteria for CAA, in the appropriate clinical context and based on MRI markers of small vessel damage.
Therapeutic implications	Acute treatment according to the clinical syndrome at presentation. Main long term goal is prevention of new lobar ICH (recurrent or incident), by blood pressure management and avoiding antithrombotics unless a compelling indication exists. Cognitive rehabilitation in mild cognitive impairment/dementia.	Acute treatment according to the clinical syndrome at presentation. Control of vascular risk factors. Cognitive rehabilitation in vascular cognitive impairment/dementia. Safety of antithrombotic use is of lesser concern compared to CAA patients.

CMB = cerebral microbleed; cSS = cortical superficial siderosis.

as the motive force and biochemical interactions with basement membranes (Schley *et al.*, 2006; Morris *et al.*, 2016) that drive clearance countercurrent to blood flow (Boche *et al.*, 2008; Carare *et al.*, 2008). As perivascular drainage pathways progressively fail with age (possibly in combination with *APOE* $\epsilon 4$ or $\epsilon 2$ alleles or other pathological conditions), amyloid- β is increasingly trapped in the perivascular compartment allowing for increased aggregation and deposition along the basement membranes of small arteries. It is plausible that this failure in the cortex and resultant stagnation of interstitial fluid might lead to enlargement or dilation of perivascular spaces (also termed Virchow-Robin spaces) in the underlying white matter (Weller *et al.*, 2015). In CAA, enlarged perivascular spaces often become visible on standard clinical MRI sequences, preferentially in the centrum semiovale (*i.e.* cerebral white matter) (Roher *et al.*, 2003; Charidimou *et al.*, 2013*b*, 2014; Martinez-Ramirez *et al.*, 2013; van Veluw *et al.*, 2016). In line with this, a recent PET-MRI study suggested that high centrum semiovale perivascular spaces are associated with higher median cortical PiB retention across a wide range of cerebrovascular amyloid deposition (Charidimou *et al.*, 2015*a*).

A model on cause and effect for the perivascular drainage-amyloid accumulation hypothesis is not yet available. Nevertheless, perivascular drainage impairment potentially sets in motion a self-reinforcing pathway by which worsening vascular amyloid- β accumulation leads to activation of

vascular injury pathways, impaired vascular physiology, and further increased parenchymal and vascular amyloid- β accumulation (through a ‘feed-forward loop’ of reducing drainage efficiency) (Hawkes *et al.*, 2011; Arbel-Ornath *et al.*, 2013) (Fig. 2). Mouse model studies from multiple research groups have highlighted the potential importance of this pathway. Interruption of vascular pulsation by photocoagulation markedly reduces perivascular clearance (Arbel-Ornath *et al.*, 2013) and increases local amyloid- β accumulation as plaques and CAA (Garcia-Alloza *et al.*, 2011). The kinetics of CAA development are not well established, but vascular amyloid- β progresses mostly by propagation, which results in narrowing of unaffected gaps in small vessels (Robbins *et al.*, 2006; Kimbrough *et al.*, 2015) and expansion of amyloid- β from the basement membranes to progressively replace all tissue elements in the artery wall (Keable *et al.*, 2016).

Another intriguing possibility is that the evolving pathophysiology of CAA is reflected and partly driven by specific alterations in the array of vascular gene expression (or vasculome) over time (Guo *et al.*, 2012). Recent findings suggest that perturbations in the vasculome may mediate both brain function and injury. For example, under normal conditions, the endothelium can provide signals that support neurogenesis (Shen *et al.*, 2004; Ohab *et al.*, 2006), protect neurons against stress (Guo *et al.*, 2008), and mediate homeostasis in oligodendrocyte precursor pools (Arai and Lo, 2009). When activated by injury, the endothelium

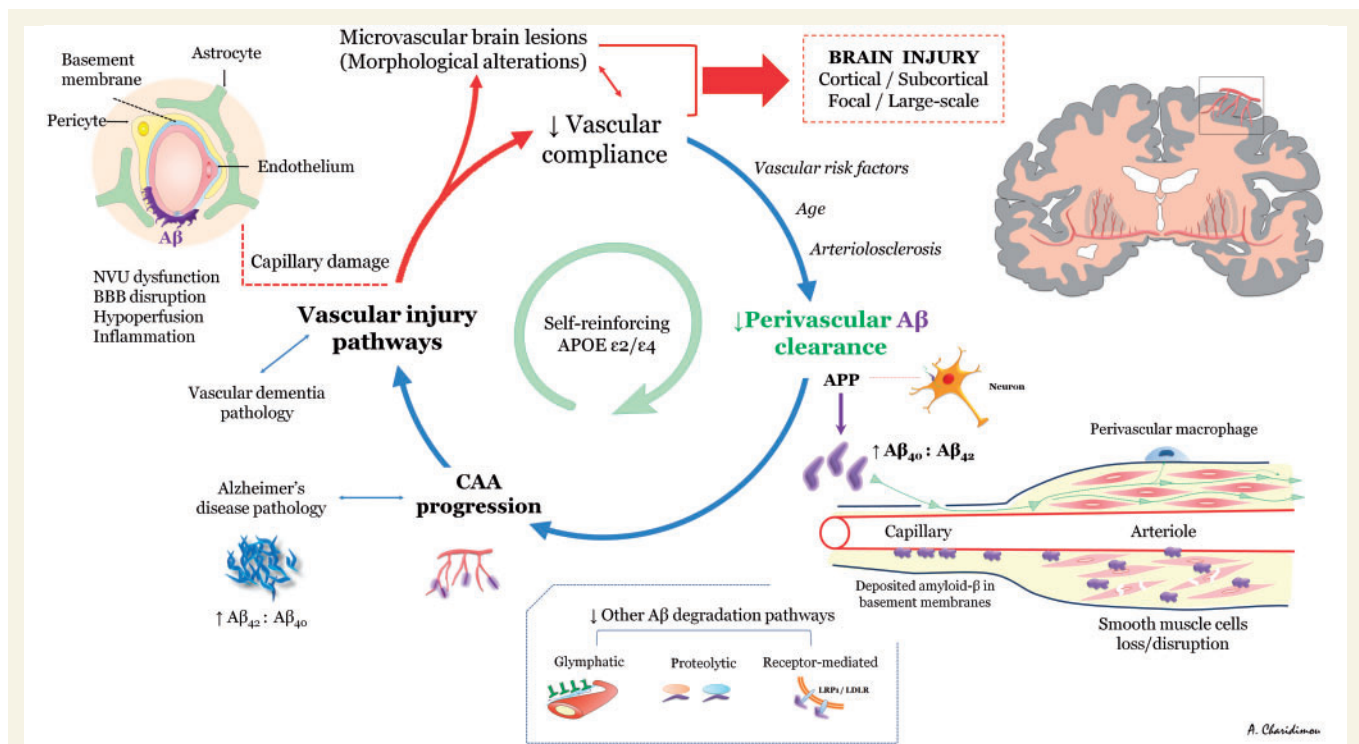


Figure 2 Schematic overview of potential mechanisms of CAA pathophysiology as a self-reinforcing process. See text for details. A β = amyloid- β ; BBB = blood–brain barrier; NVU = neurovascular unit.

can produce pro-inflammatory cytokines that magnify neuroinflammation and secondary injury (Pober and Sessa, 2007), disrupt endothelial tight junctions and basal lamina with blood–brain barrier breakdown (Rosenberg and Yang, 2007; Sandoval and Witt, 2008), and alter vessel physiology. It has also been suggested that amyloid might propagate and be transmitted in a prion-like fashion, but this is an active area of investigation (Jaunmuktane *et al.*, 2015; Frontzek *et al.*, 2016). At what ‘tipping-point’ CAA starts to propagate more CAA, potentially setting in motion this vicious cycle, is currently unknown.

The key molecular and physiological steps involved in damaging small vessels and retarding amyloid clearance, as well as the importance of these pathways in human cerebrovascular amyloid- β accumulation, have yet to be elucidated. At a neuropathological level, advanced CAA is associated with important morphological changes including loss of vascular smooth muscle cells (Dotti and De Strooper, 2009) and replacement with amyloid- β deposits, often markedly thickening the vessel wall (Mandybur, 1986; Vonsattel *et al.*, 1991a; Greenberg *et al.*, 2009a) or even vessel occlusion (Olichney *et al.*, 1995) and loss of compliance leading to brittle, fragile vessels prone to microaneurysm formation and leakage (Attems *et al.*, 2011). Cerebrovascular compliance is an almost entirely uncharacterized aspect of small vessel disease, but a candidate mediator of reduced perivascular clearance (Weller *et al.*, 2008). The loss and distortion of the normal anatomical elements of the vessel wall in CAA presumably trigger the various types of structural focal—mainly cortical—brain lesions such as ICH, cerebral microbleeds, siderosis and microinfarcts.

Capillaries and neurovascular dysfunction in cerebral amyloid angiopathy

Amyloid- β was recently shown to be highly toxic to pericytes, which, in turn, are important to blood–brain barrier function, basement membrane maintenance, and play a key role for neurovascular coupling (Hall *et al.*, 2014). The distribution of capillary flows was also recently demonstrated to determine oxygen extraction efficiency (Jespersen and Ostergaard, 2012), implying that capillary pathology can be a source of tissue hypoxia and neuronal injury—even in the absence of flow-limiting pathology *per se* or structural alterations (Ostergaard *et al.*, 2016). Whether these findings have specific implications in CAA has not yet been investigated directly, but data from the Alzheimer’s disease field are compelling (Zlokovic, 2011; Nelson *et al.*, 2016). However, they do raise the possibility that amyloid- β deposition at the level of the capillaries might lead to degenerative changes by two mechanisms: (i) interfering with various elimination pathways, including the perivascular drainage pathway, clearance at the blood–brain barrier, or impairing the transendothelial clearance

(Fig. 3); and (ii) affecting the metabolism of brain tissue (Kumar-Singh, 2009).

Cortical thinning in cerebral amyloid angiopathy

Of major interest, a recent study provided strong evidence of CAA-related cortical atrophy independent of Alzheimer’s disease (Fotiadis *et al.*, 2016). Though the mechanism for this association is not well defined, the average cortical width of 63 non-demented CAA subjects versus 63 age-matched healthy control subjects was reduced (2.17 ± 0.11 mm in CAA versus 2.31 ± 0.07 mm in controls, $P < 0.001$) (Fotiadis *et al.*, 2016) (Fig. 3A). A similar finding was observed in subjects with Dutch-type hereditary CAA, a condition characterized by severe CAA but little or no Alzheimer’s disease pathology (Natte *et al.*, 2001). The average cortical thickness of 26 Dutch-type hereditary CAA subjects was significantly lower than age-matched healthy controls (2.31 ± 0.18 mm versus 2.42 ± 0.10 mm, $P = 0.006$) (Fotiadis *et al.*, 2016). Greatest thinning was noted in medial frontal and posterolateral brain regions, a somewhat different pattern from the primarily limbic and multimodal association regions with greatest thinning in Alzheimer’s disease (Dickerson *et al.*, 2009). The clinical implications of cortical thinning in CAA and its relation to cognitive impairment requires further study.

Altered vascular reactivity

CAA appears to have substantial effects on vascular function/physiology, which might result in more widespread brain injury (Smith and Greenberg, 2009; Pantoni, 2010). Amyloid deposition in the vessel wall may cause gliovascular unit impairment (Kimbrough *et al.*, 2015), endothelial dysfunction (Grinberg *et al.*, 2012), impaired autoregulation and blood–brain barrier disruption (Attems *et al.*, 2011). One key candidate mechanism suggested by transgenic animal studies is impaired cerebrovascular compliance and reactivity to physiological stimuli (Niwa *et al.*, 2000; Shin *et al.*, 2007; Han *et al.*, 2008; Park *et al.*, 2013). The brain microvasculature forms interconnected vascular networks (a 2D network of pial arterioles that connects to a 3D network of subsurface microvessels) (Blinder *et al.*, 2013; Shih *et al.*, 2015); the practical consequence is that apparently unaffected microvessels might still contribute to the overall CAA-related tissue injury by indirect consequences from neighbouring amyloid-laden microvessels (Shih *et al.*, 2013).

The best established physiological change in individuals with advanced CAA is reduced vasodilation to physiological stimuli. This finding has been demonstrated in studies measuring the functional MRI blood oxygen level-dependent (BOLD) response to visual stimulation (Dumas *et al.*, 2012b; Peca *et al.*, 2013) (Fig. 3B), which take advantage of the occipital predominance of CAA (Vinters and Gilbert, 1983). In non-demented CAA patients, the

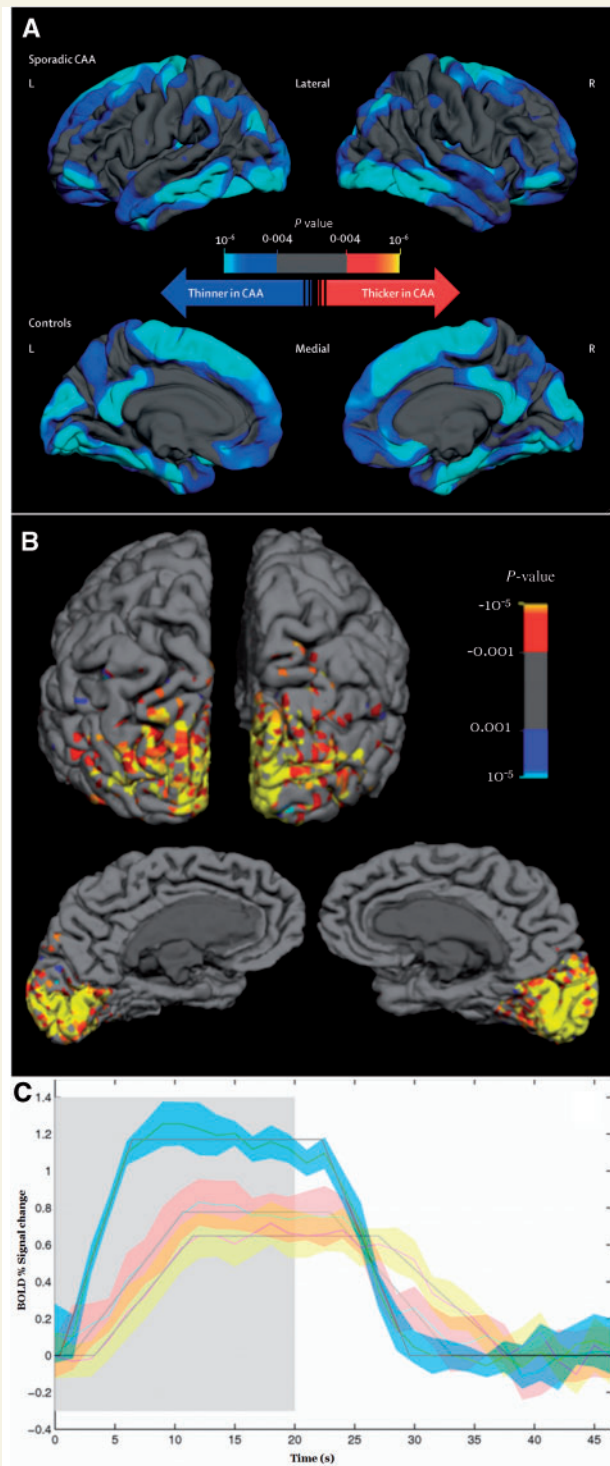


Figure 3 Cortical thickness and functional MRI measures in cerebral amyloid angiopathy. (A) Regional differences in cortical thickness between patients with sporadic CAA and their age-matched controls (Fotiadis *et al.*, 2016, reproduced with permission). Topographic surface maps were generated based on a general linear model (adjusting for age and sex) using a threshold of $P < 0.01$ (with false discovery rate correction for multiple comparisons) (Fotiadis *et al.*, 2016). The resulting maps show the statistically significant regional differences in cortical thickness between the two groups. (B) Functional MRI visually activated region of interest of a representative probable CAA subject. The colour scale

functional MRI response showed 27–28% reduced peak amplitude, 73% longer time to peak, and 42% longer time to return to baseline compared with elderly control subjects matched for age (Dumas *et al.*, 2012b; Peca *et al.*, 2013) (Fig. 3C). Altered BOLD response might be driven by vascular or neuronal dysfunction, but the findings that CAA patients and control individuals had similar visual evoked response amplitude (Peca *et al.*, 2013) and that results were consistent in secondary analyses restricted to responding voxels only (Dumas *et al.*, 2012a), suggest that the differences are largely driven by effects of CAA on the vessels themselves. A longitudinal analysis also showed declining amplitude in BOLD response to visual stimulation among CAA subjects (Switzer *et al.*, 2016) (Fig. 3C). These studies also showed associations between impaired functional MRI response and white matter hyperintensity volume, suggesting mismatched blood supply versus tissue demand as a potential mechanism mediating CAA-related tissue damage. Another finding consistent with this possibility is that cortical thickness is negatively correlated with the time to peak BOLD response to visual stimulation ($r = -0.4$, $P = 0.005$ with adjustment for covariates) (Fotiadis *et al.*, 2016).

Microstructural damage and brain network alterations

CAA-related perfusion impairment may be responsible not only for subcortical white matter lesions (Gurol *et al.*, 2013) but also for tissue microstructural changes detected by diffusion tensor imaging (Salat *et al.*, 2006; Reijmer *et al.*, 2015) and microinfarcts (Reijmer *et al.*, 2016b). Analysis (Fig. 4A) of the local network parameter node strength (the sum of fractional anisotropy-weighted connections attached to a given node) found locally altered network structure in CAA subjects compared to controls, particularly in occipital, posterior parietal, and posterior temporal cortex (Fig. 4B), resembling the distribution of CAA pathology (Reijmer *et al.*, 2015). Network disturbances were associated with worse cognitive functioning and amyloid load on PET, providing direct links between vascular amyloid and impairments in white matter connectivity (Reijmer *et al.*, 2015). Punctate diffusion-weighted imaging lesions (presumably corresponding to acute

Figure 3 Continued

denotes the Z-statistic for activation using the canonical haemodynamic response function. (C) Functional MRI measurements in response to visual stimulation in an elderly probable CAA patient (red error space) versus an age-matched control subject (blue error space). For the CAA patient, functional MRI was done at baseline (red error space) and again with the same scanner and protocol after one clinically asymptomatic year (yellow error space). The solid lines represent the change from baseline BOLD signal averaged over 16 cycles of visual stimulation (on 20 s, shaded region, then off 28 s), with standard deviations of the responses shown in blue, red and yellow spaces and the trapezoidal model fits, as previously described (Dumas *et al.*, 2012a). In the CAA patient, the amplitude

microinfarcts) in subcortical white matter have been demonstrated to produce focal changes in mean diffusivity and fractional anisotropy (Auriel *et al.*, 2014), raising the idea that altered diffusivity may partly reflect the cumulative effect of cerebral microinfarcts or other focal lesions on cortical microstructure. Brain network alterations in patients with CAA ($n = 33$) appear to worsen measurably over just 1.3-year follow-up, progressing from posterior to frontal regions with increasing disease severity; this decline is associated with worse executive functioning (Beta = 0.41, $P = 0.04$) (Reijmer *et al.*, 2016a). Of note, CAA patients included in all the aforementioned *in vivo* studies were symptomatic with high vascular lesion burden. A relevant question is whether advanced imaging techniques can also detect CAA-related abnormalities

before the disease becomes symptomatic (Akoudad *et al.*, 2013). This approach is currently limited, however, by our poor understanding of tissue-level pathological basis (Fig. 4C) of the various neuroimaging abnormalities discussed, making it difficult to link these large-scale measures to any specific pathogenic process or parenchymal injuries.

Towards mapping different cerebral amyloid angiopathy phenotypes

It is becoming increasingly evident that CAA is not a uniform, but rather a complex and very heterogeneous entity

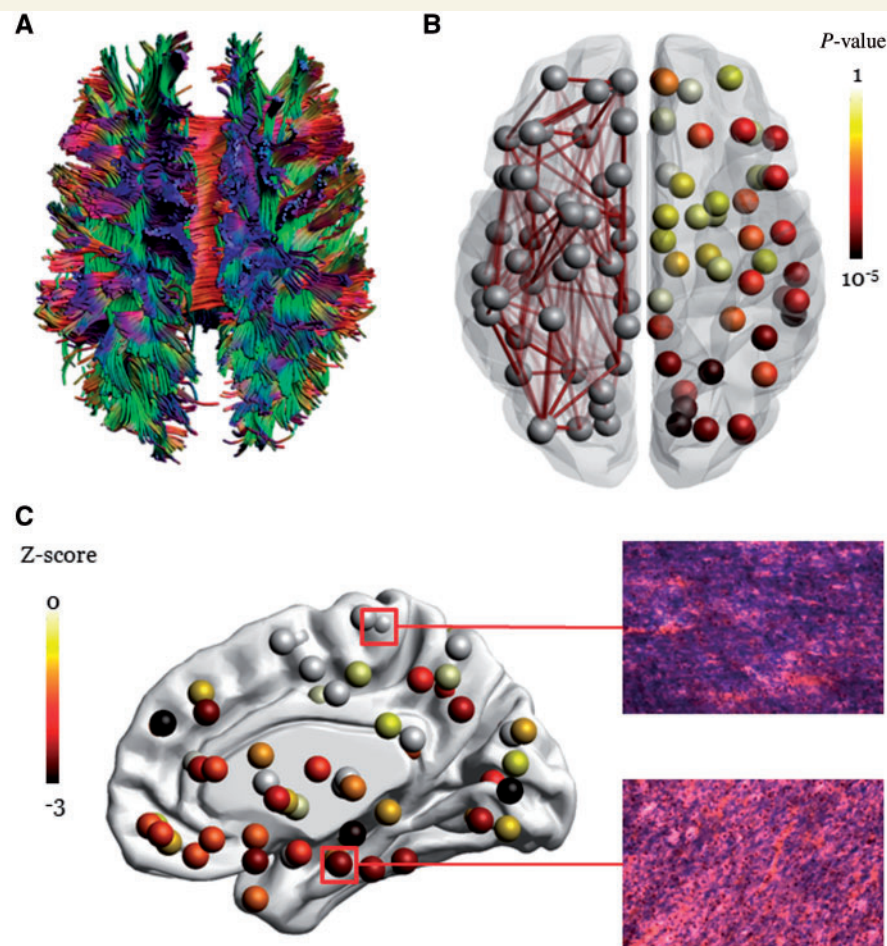


Figure 4 White matter injury in CAA detected with diffusion tensor imaging. (A) Whole brain fibre tract reconstruction from fractional anisotropy map reflecting the degree of anisotropic diffusion of water molecules. (B) Left hemisphere: visualization of a DTI-based brain network from a patient with severe CAA. Brain regions are depicted by nodes and fibre tracts between regions are depicted by edges. Right hemisphere: local differences in connectivity strength between patients with CAA compared to age-matched controls, as previously described (Reijmer *et al.*, 2015). Results show that tracts projecting to occipital, parietal, and temporal regions are most affected, whereas tracts projecting to frontal and subcortical regions are relatively spared (darker nodes show greater differences from controls). (C) Regions marked in red were selected for histopathological evaluation of an autopsied CAA subject who underwent DTI scanning during life. The white matter near a region of reduced nodal strength showed considerable myelin loss on Luxol[®] Fast Blue stained sections relative to a region of relatively reserved nodal strength.

that can follow several different pathways (Figs 5 and 6). While sporadic CAA is commonly found in the elderly (Keage *et al.*, 2009), it is usually mild and clinically silent. In the fraction of patients with CAA that will go on to develop clinical symptoms, the sentinel presentations of the disease vary (Greenberg *et al.*, 1993; Maia *et al.*, 2007), while each presentation is associated with its own cluster of biomarkers (Table 2). It follows that the clinical and imaging heterogeneity and phenotypes of the disease might be reflecting distinct neuropathological subtypes or patterns of cerebrovascular amyloid deposition (Fig. 5) and activation of diverging pathophysiological cascades. Mild CAA, a common finding in elderly and Alzheimer's disease brains, likely reflects the perivascular drainage impairment accompanying ageing. Severe CAA is generally assumed to result in the symptomatic sentinel presentations of the disease. However, the pattern on amyloid deposition in severe CAA varies greatly with differing anatomical patterns of deposition and degrees of accumulation and progression (Fig. 6) (Keable *et al.*, 2016). The spectrum ranges from amyloid co-localization with basement membranes, to replacement of smooth muscle cells by amyloid with some preservation of basement membrane elements, to complete replacement of the artery wall by amyloid (Fig. 6) (Keable *et al.*, 2016). Yet, in some arterioles, amyloid deposition

remains focal, even to the point of complete replacement of smooth muscle layers and basement membrane (Keable *et al.*, 2016). The focal complete replacement of the vessel wall by amyloid might provide a potential site of weakness leading to haemorrhage. In other cases, deposition of amyloid is seen in the tunica adventitia surrounding the perimeter of the vessel (instead of the tunica media), which may represent an additional part of the lymphatic drainage pathway (Keable *et al.*, 2016). Adding another dimension to the spectrum of the disease, these patterns of amyloid deposition may differentially affect leptomeningeal and cortical parenchymal vessels, as well as capillaries (Fig. 6). For example, a systems proteomic analysis demonstrated that clusterin (apolipoprotein J) and tissue inhibitor of metalloproteinases-3, co-localize with amyloid- β and seem to be upregulated in leptomeningeal (but not cortical) arteries from CAA patients compared to young and elderly controls (Manousopoulou *et al.*, 2016).

The heterogeneity in these pathological patterns and clinical imaging presentations of CAA may be influenced by how different risk factors affect the process of perivascular clearance and brain injury during the disease process (Fig. 2). For example, APOE $\epsilon 4$ alters the biochemical composition of basement membranes and is involved in various amyloid degradation systems, whereas APOE $\epsilon 2$ promotes

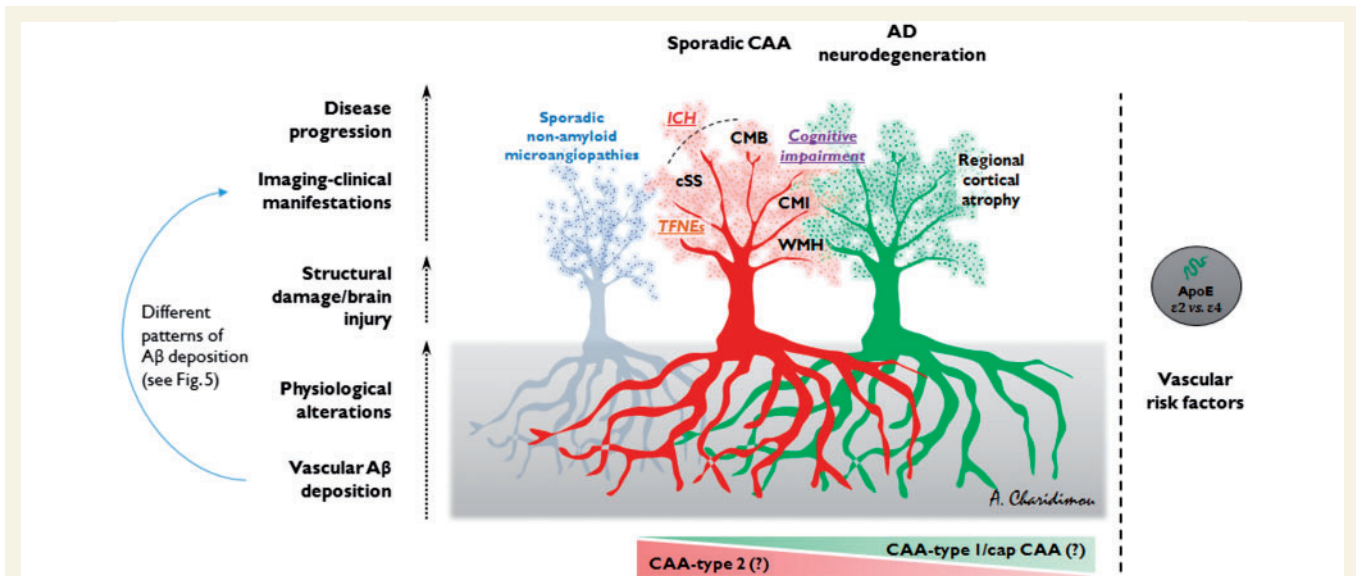
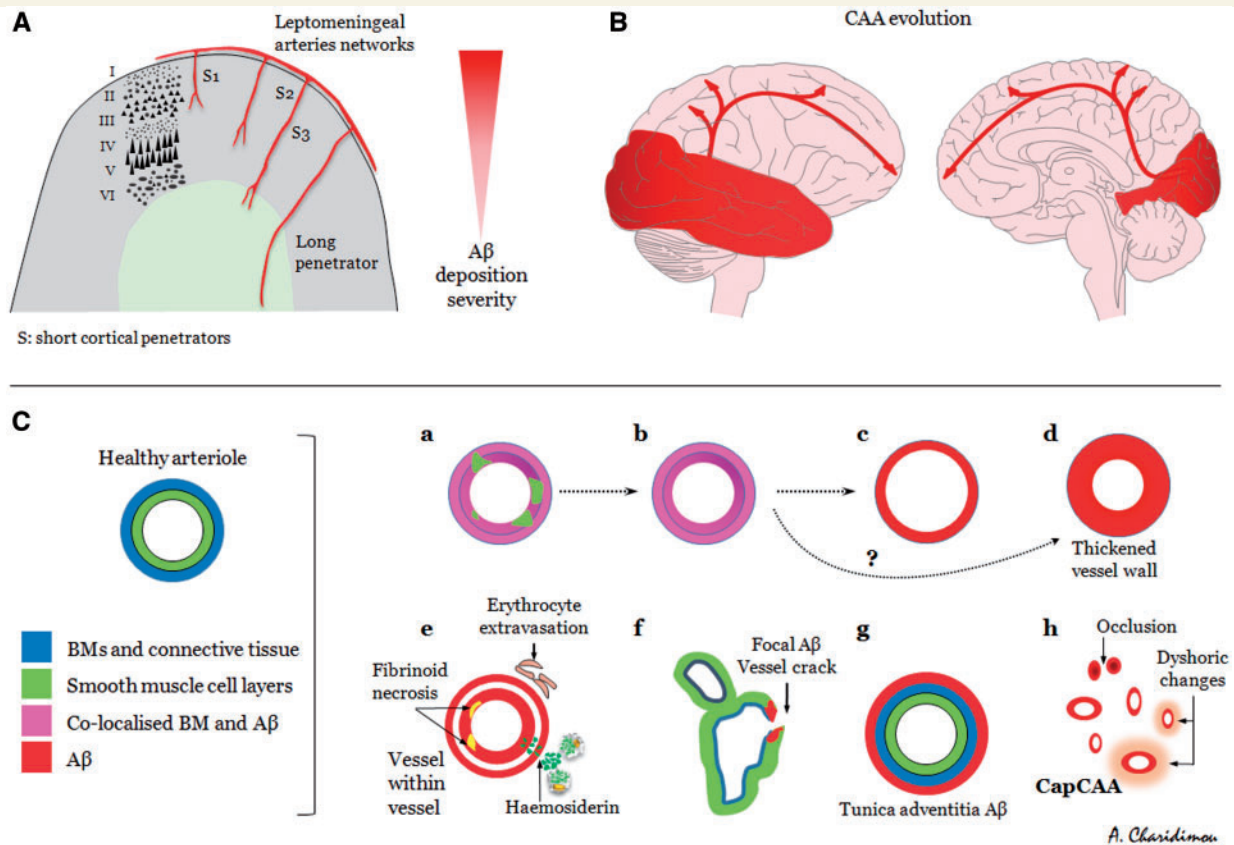


Figure 5 Suggested heuristic schematic of the possible different phenotypes of CAA and directions in the expression of the disease. The two main trees (from right to left) depict Alzheimer's disease (AD) neurodegeneration, in which CAA is commonly found, and sporadic CAA. The third tree, in the background, represents sporadic non-amyloid microangiopathies. All three pathologies often co-exist in different combinations and severity in the ageing brain. Initially, different but overlapping pathophysiological pathways (roots of each tree in the grey box) can result in progressive vascular amyloid accumulation and pathophysiological alterations, which might culminate in structural vascular damage and brain injury. In extreme forms these might result in different neuroimaging and clinical phenotypes of the disease (different branches in each tree). At the one end we have the primarily haemorrhagic types of CAA, predominantly characterized by either multiple lobar cerebral microbleeds (CMB) (i.e. 'microbleeders') or cortical superficial siderosis (cSS) ('superficial bleeders'); and/or symptomatic ICH (i.e. 'macrobleeders'); at the other end we have the less haemorrhagic phenotypes of CAA, clinically expressed with more cognitive impairment and probably more strongly associated with cortical microinfarcts (CMI), with or without Alzheimer's disease. Many patients can have intermediate phenotypes of the disease. The APOE ϵ genotype and vascular risk factors likely influence all the critical steps and different directions taken during the course of the disease in the ageing brain. A β = amyloid- β ; TFNEs = transient focal neurological episodes; WMH = white matter hyperintensity.



structural vasculopathic changes in amyloid-laden vessels, making them more prone to rupture. Mid-life hypertension might alter the biophysical forces acting upon the arterial wall, modifying the motive force for perivascular clearance but also the structural integrity of the vessels (in combination with sporadic non-amyloid microangiopathic alterations). Other potential risk factors and comorbid conditions that result in vessel rupture associated with CAA remain unclear. Of note, the degree of vessel wall replacement by amyloid required before the vessel ruptures is currently unknown.

A number of observations from clinical-MRI CAA cohorts can shed further light on the concept of different disease phenotypes. An interesting study suggested that multiple lobar microbleeds associated with CAA-related pathology might in some respects differ from macrobleeds, since they have a bimodal (rather than continuous) size distribution on MRI (Greenberg *et al.*, 2009a). In a patient subset that underwent autopsy, those with high microbleed counts ('microbleeders') had increased wall thickness of amyloid-laden vessels compared to patients with relatively low microbleed counts and lobar ICH ('macrobleeders')

(Greenberg *et al.*, 2009a). A recent MRI-neuropathological studies recruited 105 patients with CAA pathologic confirmation and *in vivo* MRI and compared pathologic, imaging, and *APOE* genotype data between subjects with versus without symptomatic ICH. The two groups had similar CAA burden, almost all pathology samples had neuritic plaques, whereas neurofibrillary tangles were more commonly present in the patients without intracerebral bleeds (87% versus 42%, $P < 0.0001$). Disseminated cortical superficial siderosis was considerably more common in patients with ICH (33.3% versus 5.9%, $P < 0.0001$) and was associated with *APOE* $\epsilon 2$ (but not *APOE* $\epsilon 4$) (Charidimou *et al.*, 2015c). Surprisingly, cortical superficial siderosis, which confers a high risk of future lobar ICH, is not associated with lobar microbleeds (Charidimou *et al.*, 2013a; Shoamanesh *et al.*, 2014). A plausible explanation is that siderosis predominantly reflects a severe leptomeningeal pattern of amyloid deposition rather than deeper cortical CAA, which manifests itself more with microbleeds. Although studies of CAA phenotypes often focus on the extreme forms (such as microbleeders, macrobleeders, siderobleeders, etc.), many patients likely fall into a mixed category in which various CAA-related vascular processes co-exist.

Although literature to support firm conclusions remains extremely limited, a ‘phenotype approach’ in CAA may provide a conceptual model allowing greater reliance on different clusters of clinical and pathophysiologically relevant MRI biomarkers in future CAA trials and patient management (Fig. 6) (Greenberg *et al.*, 2014).

Implications for patient management in cerebral amyloid angiopathy

The management of acute CAA-related ICH is the same as any spontaneous ICH, and it is summarized in the American Heart Association/American Stroke Association (Hemphill *et al.*, 2015) and the European Stroke Organization (Steiner *et al.*, 2014) guidelines. To date, there is no disease-specific CAA treatment, and hence the long-term management of CAA patients is centred on the prevention of incident or recurrent haemorrhagic events and dementia. In this context, an important first step in decision-making for certain drug use or avoidance (antithrombotics, statins etc.) and other interventions is identifying the probability that a given patient with spontaneous ICH has CAA. In this setting, an accurate assessment of haemorrhage risk based on the presumed cause of ICH and/or the predominant type/severity of the underlying haemorrhage-prone microangiopathy. A key difference between the two broad types of small vessel disease and aetiologies of spontaneous ICH is the much higher annual recurrence rate in CAA-related lobar ICH compared to sporadic non-amyloid microangiopathy-related ICH

(~10%/year versus 2–3%/year, respectively). Furthermore, the risk of incident dementia after ICH appears to be more than two times higher in patients with lobar (incidence at 1 year: 23.4%; 95% CI: 14.6–33.3) than for patients with non-lobar ICH (incidence at 1 year: 9.2%; 95% CI: 5.1–14.7) (Moulin *et al.*, 2016).

A common approach for CAA patients with a previous history of lobar ICH is to avoid antithrombotic treatment as much as possible, as they might increase the risk of recurrence (Eckman *et al.*, 2003; Hofmeijer *et al.*, 2015). Even for strong indications such as non-valvular atrial fibrillation, oral anticoagulation with warfarin may be generally unsafe following CAA-related ICH (Eckman *et al.*, 2003), although thus far, large observational data are missing. American Heart Association/American Stroke Association guidelines recommend avoiding oral anticoagulation in patients with lobar ICH, but to consider resuming oral anticoagulation in patients with non-lobar ICH (Hemphill *et al.*, 2015). The role of antiplatelet agents and their systematic discontinuation or not in CAA-related ICH patients remains a hotly debated topic (Al-Shahi Salman and Dennis, 2014; Falcone and Rosand, 2014). The RESTART randomized trial (<http://www.restarttrial.org/>) is underway to provide some answers on whether to avoid antithrombotic use after an ICH. Another option for those CAA-related ICH patients requiring anticoagulation might be newer oral anticoagulants, which have been shown to have lower overall ICH risk. For example, apixaban has a similar intracranial bleeding risk profile as aspirin, but is more effective at reducing ischaemic stroke risk (Connolly *et al.*, 2011). The relative risks are less clear for individuals with asymptomatic lobar microbleeds or cortical superficial siderosis only, fulfilling the Boston criteria for CAA. In this situation, clinicians should carefully weigh risk-benefit for recurrent ischaemic stroke versus haemorrhagic complications. Larger, more definitive studies (Charidimou *et al.*, 2015e) and randomized trials are required to settle these important questions.

Although CAA is not thought to be directly linked to hypertension, strict control of blood pressure within the normal range is recommended, especially after an ICH. A subgroup analysis of the PROGRESS trial (Arima *et al.*, 2010) demonstrated that lowering blood pressure with the antihypertensive drug perindopril (with or without indapamide) reduced the risk of probable CAA-related ICH recurrence by 77% (95% CI, 19%–93%) over a follow-up period of 3.9 years. Recently, inadequate blood pressure control in ICH patients from a large single centre observational study was associated with hazard ratios of 3.53 (95% CI, 1.65–7.54) for recurrent lobar ICH and of 4.23 (95% CI, 1.02–17.52) for non-lobar ICH when compared to those with adequately controlled blood pressure (Biffi *et al.*, 2015). These and other observations strongly support the need for strict and continued blood pressure control in CAA patients, which might impact outcomes such as recurrent ICH, cognitive impairment, or progression of small vessel disease pathology. Finally, supportive

care, lifestyle modifications and, in patients with recent CAA-related ICH, cognitive rehabilitation may maximize function and enhance recovery.

Future perspectives

There is currently a growing interest in CAA with an explosion of publications in the last 15 years and dense collaboration networks between research teams in the field (Charidimou *et al.*, 2016a). International efforts aimed at translating mechanistic insights into novel treatment approaches (Al-Shawi *et al.*, 2016), including an ongoing first-of-kind CAA anti-amyloid immunotherapy trial with ponezumab, an anti-amyloid- β_{40} selective antibody (NCT 01821118) are underway (Greenberg *et al.*, 2014). The rationale for anti-amyloid immunotherapy in CAA is to attenuate amyloid accrual in cerebral vessels and by doing that restore vascular reactivity in the short-term and prevent the occurrence of clinical symptomatology in the long-term (Bales *et al.*, 2016). Rapidly accumulating data on *in vivo* detection of the pathogenic steps involved in CAA offers substantial promise for future trials aimed at identifying disease-modifying treatments (Saito and Ihara, 2014) for this largely untreatable disease. Nonetheless, there are many remaining ‘known unknowns’ on all the postulated steps in CAA pathogenesis and neurological dysfunction, ranging from vascular amyloid deposition itself to physiological alterations, haemorrhagic and non-haemorrhagic (cortical and subcortical) structural damage, symptomatic ICH, and presentations without major haemorrhage, including cognitive dysfunction. It is anticipated, that shedding light on these aspects may also have implications for other small-vessel disease processes in the ageing brain and vascular cognitive impairment.

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