







Invited Review: The spectrum of age-related small vessel diseases: potential overlap and interactions of amyloid and nonamyloid vasculopathies

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Invited Review: The spectrum of age-related small vessel diseases: potential overlap and interactions of amyloid and nonamyloid vasculopathies

Deep perforator arteriopathy (DPA) and cerebral amyloid angiopathy (CAA) are the commonest known cerebral small vessel diseases (CSVD), which cause ischaemic stroke, intracerebral haemorrhage (ICH) and vascular cognitive impairment (VCI). While thus far mainly considered as separate entities, we here propose that DPA and CAA share similarities, overlap and interact, so that ‘pure’ DPA or CAA are extremes along

a continuum of age-related small vessel pathologies. We suggest blood-brain barrier (BBB) breakdown, endothelial damage and impaired perivascular β -amyloid ($A\beta$) drainage are hallmark common mechanisms connecting DPA and CAA. We also suggest a need for new biomarkers (e.g. high-resolution imaging) to deepen understanding of the complex relationships between DPA and CAA.

Keywords: blood-brain barrier, cerebral amyloid angiopathy, cerebral small vessel diseases, deep perforator arteriopathy, hypertensive arteriopathy, β -amyloid drainage

Introduction

Sporadic cerebral small vessel diseases (CSVD) are the commonest known pathological processes to affect the ageing brain. The two most common forms are deep perforator arteriopathy (DPA; also known as hypertensive arteriopathy or nonamyloid CSVD) and cerebral amyloid angiopathy (CAA). They are highly prevalent

in the elderly: about 80% of those over 65 years old and nearly all of those over 90 years old show clinical or radiological manifestations of CSVD [1]. DPA and CAA are not only major causes of ischaemic stroke and intracerebral haemorrhage (ICH) but also play key roles in cognitive decline and dementia.

Sporadic CSVD has attracted increasing attention, in part due to the ease with which modern imaging (particularly magnetic resonance imaging (MRI)) can detect its manifestations in the brain, including white matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMB) and enlarged perivascular spaces (PVS). Although several recent comprehensive reviews of the

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pathology, neuroimaging and clinical effects of CSVD are available [2–5], there has been less interest in how DPA and CAA coexist and interact. Understanding the probable overlap, pathophysiological and clinical interactions of two sporadic CSVD entities is potentially important to improve our understanding of the clinical impact, and optimal treatment, of CSVD. In this article, we first consider DPA and CAA separately, before considering their similarities, and how they overlap and might interact. We hypothesize that (pure) DPA and (pure) CAA represent the extremes of a continuum of age-related small vessel pathology, focusing on early endothelial damage and amyloid clearance disturbances as potential mechanisms linking the two processes.

The consideration of several hereditary DPA or CAA variants is beyond the scope of this review and for this purpose we refer to further excellent reviews [1,6–8].

Deep perforator arteriopathy and cerebral amyloid angiopathy

DPA mainly affects small arteries, veins, arterioles, venules and capillaries originating as deep perforating vessels from large vessels of the base of the brain or as penetrating cortical or medullary vessels from superficial medium sized arteries [9]. Pathologically, DPA is characterized by arteriosclerosis, fibrinoid necrosis and lipohyalinosis (Figure 1A), describing endothelial proliferation, tunica media degeneration and overall small vessel wall thickening [10]. Endothelial and blood-brain barrier (BBB) dysfunction seems to play a major role in DPA initiation. This is indicated by a reduction of endothelial tight junctions and leakage of proteins into and surrounding the small vessel walls in young experimental DPA models [11–14]. Because of its most common relation to age and arterial hypertension (aHTN), DPA has been also called age or vascular risk factor-associated CSVD [2,9]. However, around 30% of the cognitively normal elderly reveal features of DPA on brain imaging in the absence of aHTN [15], clearly questioning the often incorrectly assumed obligate relationship between hypertension and DPA [5,16].

Sporadic (noninflammatory) CAA is specifically characterized by the progressive deposition of mainly amyloid β 40 (A β 40) protein (and, to a lesser extent, A β 42): (i) in the walls of capillaries and the surrounding neuropil ('dysphoric changes') referred to as

capillary CAA (CAA-type 1), and (ii) in noncapillary blood vessels such as parenchymal and leptomeningeal small to medium sized arteries, arterioles and rarely veins (CAA-type 2) (Figure 1B,C) [17]. Vascular A β accumulation initiates at the abluminal aspects of the smooth muscle cells basal membranes (BM), resulting in tunica media and entire small vessel wall degeneration (vessel wall splitting, fibrinoid necrosis). CAA is first found in cortical regions (mainly occipital (calcarine) cortex), including the grey-white matter junction; it secondly affects allocortical and cerebellar vessels, and finally it can be found in the deep grey and white matter [17]. The most commonly used diagnostic criteria for CAA are the modified Boston criteria, relying on neuropathological findings (if available), age (≥ 55 years), an imaging confirmed strictly lobar (cortical-subcortical) pattern of large or smaller haemorrhages, and the exclusion of competing causes of cerebral haemorrhages [18].

CAA-related inflammation (CAA-ri) is a rarer variant characterized by an immune response to the vascular deposits of A β , which compared to noninflammatory sporadic CAA displays more widespread MRI pathologies (WMH, CMB) and lymphocytes/macrophages within/surrounding the A β -laden vessels (Figure 1G–I) [19,20]. Compared to noninflammatory CAA, CAA-ri is treatable showing a favourable response to the application of either steroids and/or cyclophosphamide [21].

For further details regarding the pathological and pathophysiological aspects of DPA and CAA, we refer to several recent excellent reviews [2–5].

Neuroimaging biomarkers of sporadic CSVD

DPA is associated with various haemorrhagic and non-haemorrhagic neuroimaging biomarkers, several of which are also found in sporadic CAA. Haemorrhagic biomarkers include spontaneous ICH, CMB, cortical superficial siderosis (cSS), which are best detected on susceptibility-weighted imaging and T2*-weighted gradient recalled echo MRI sequences, and atraumatic convexity subarachnoid haemorrhage (cSAH), best seen on acute noncontrast computed tomography (CT) or fluid-attenuated inversion recovery (FLAIR) MRI sequences. Nonhaemorrhagic biomarkers, on the other hand, comprise lacunes of presumed vascular origin; diffusion-weighted imaging (DWI) hyperintensities

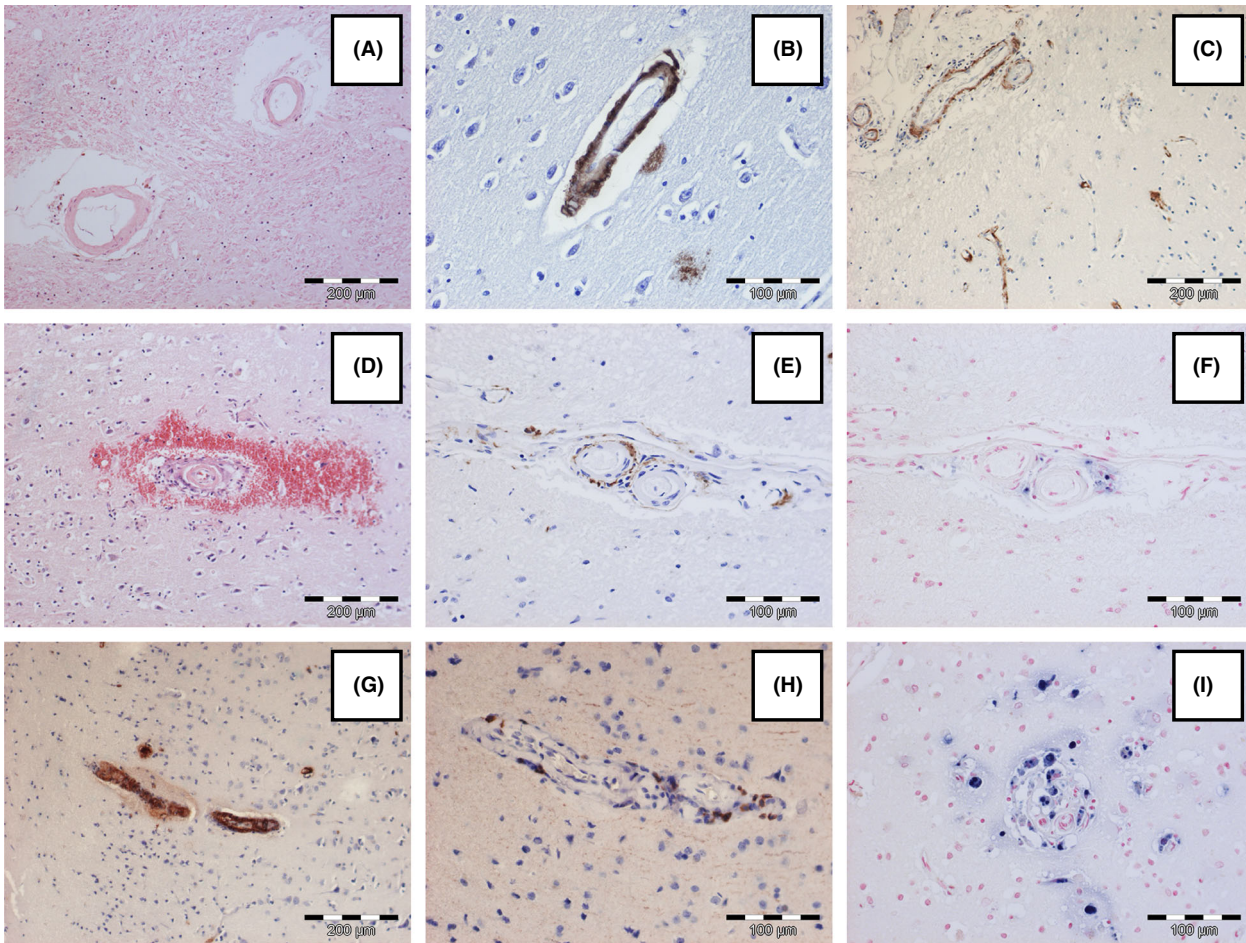


Figure 1. Microscopic features of small vessel disorders in autopsy brain tissue. (A) Deep perforator arteriopathy with thickening of the small blood vessels and enlargement of perivascular spaces (H&E stain). (B) Cerebral amyloid angiopathy (CAA) is characterized by the deposition of β -amyloid (A β) in the walls of small blood vessels. A β deposition is also seen in small plaques (β -amyloid immunostaining). (C) CAA affects several leptomeningeal (upper left part) and small parenchymal cortical blood vessels (β -amyloid immunostaining). (D) Perivascular haemorrhages around a small cortical blood vessel in CAA. (E–F) Serial sections of leptomeningeal blood vessels in CAA showing vessel wall thickening, β -amyloid deposition (E) and old haemorrhages with haemosiderin deposition around the blood vessels (F iron staining). (G–I) CAA-related inflammation (CAA-ri) with A β deposition in the blood vessel walls (G), accumulation of perivascular CD3-positive T-lymphocytes (H) (G & H are serial sections) and haemosiderin deposition (I) (iron staining).

(recent small subcortical infarcts), so-called ‘microinfarcts’; WMH of presumed vascular origin; and PVS. These CSVD MRI markers often coexist with one another as they represent different manifestations of the same underlying pathological process.

For detailed neuroimaging recommendations and for the discrimination of various CSVD features, we refer to the position paper summarizing the STandards for Reporting Vascular changes on nEuroimaging [22] and to further reviews [23–26].

DPA neuroimaging biomarkers are related to age, and often to aHTN [27,28], while CAA imaging biomarkers are related to age and apolipoprotein (APO)

E genotype (APOE ϵ 2 or APOE ϵ 4 allele carriage) [29,30]. APOE ϵ 2 status has thereby been associated with CAA-type 2 and a haemorrhagic CAA phenotype, while APOE ϵ 4 positivity has been better related to CAA-type 1 and a nonhaemorrhagic but variably inflammatory CAA phenotype, closely related to dementia [31–33]. Although there seems to be a lack of robust associations between traditional vascular risk factors and CAA, lobar CMB (see below) are consistently associated with aHTN and altered total cholesterol and triglyceride levels [34,35]. There is growing evidence that DPA is associated with genetic factors including APOE allelic variations [1,36].

Haemorrhagic CSVD biomarkers

Spontaneous ICH DPA is related to ICH in deep and nonlobar localizations (basal ganglia (Bg), internal capsule, thalami, pons) (Figure 2A), although lobar haemorrhages can also occur [37,38]. CAA is, in contrast, associated with strictly lobar ICH, mainly in the frontal and parietal lobes (Figure 3A), and only rarely with the cerebellum [16,38,39]. A recent meta-analysis found a 7.4% annual risk of recurrent ICH after CAA-related ICH, but a much lower risk of recurrence after deep DPA-associated ICH (about 1% in the same meta-analysis) [40]. Re-bleeding risk after ICH is lower with good blood pressure control [27]. Oral anticoagulation and thrombolysis are both associated with an increased risk of DPA- and CAA-related haemorrhages [41,42].

CMB CMB are homogeneous areas of signal void (hypointensities) [22]. They usually correspond to perivascular haemosiderin-laden macrophages, haemosiderin deposits, iron-positive siderophages or intact erythrocytes [43], providing evidence of red blood cell extravasation from microvascular damage (Figure 1D–F) [44]. Comparative studies between ultrahigh-resolution MRI and histopathology, however, revealed that CMB also indicate various nonhaemorrhagic CSVD pathologies (e.g. microaneurysm, vessel dissection and fibrinoid necrosis) [43,45] deeming CMB to result from both haemorrhagic and ischaemic mechanisms [46].

In DPA, cerebral CMB are commonly found in the deep grey (Bg, thalami) and white matter, and infratentorially (brainstem, cerebellum) (Figure 2B) [16,22]. A strictly lobar (cortico-subcortical) pattern of CMB (typically located most often in the occipital and temporal cortical grey matter) has high specificity for CAA

(Figure 3B) [47,48]. The burden of CAA-related lobar CMB seems to be associated with cortical position emission tomography (PET) A β load [49,50], but a recent analysis questioned the common expectation that in CAA, the ruptured vessel displays significant A β load, as microhaemorrhages were preferentially found surrounding the A β negative small vasculature [51].

Mixed CMB distributions in both deep (Bg, thalamus) and lobar regions are further hypothesized to result either from severe and widespread DPA of both the deep and cortical small vessels or from DPA together with CAA in the same patient [46,52]. Currently, there is some uncertainty how to classify patients revealing a MRI mixed CMB pattern [53], and further pathological validation of the MRI markers is needed.

CMB occurrence is overall related to a higher risk of incident haemorrhages, ischaemic strokes and microinfarcts [54,55], and to cognitive decline [56].

Cortical superficial siderosis and convexity subarachnoid haemorrhage Bleeding within the subarachnoid space, the leptomeninges and the superficial (subpial) layers of the cerebral cortex from leaking leptomeningeal CAA-laden small vessels causes cSS at the cerebral convexity (resulting from repeated small superficial haemorrhages) (Figure 3D) or atraumatic cSAH [57,58]. Siderotic tissue shows extensive ferritin deposits and neuronal accumulation of neurotoxic iron [59]. CAA is the most likely cause for cSS and cSAH in the elderly [57,60], while sporadic DPA has significantly less often been linked to cSS and SAH [4,38,61]. CSS, especially its disseminated form, and cSAH have moreover been considered as a predictor for future CAA-related ICH, often preceded by transient focal neurological episodes of spreading and short-lasting (usually < 30 minutes) paraesthesia, numbness or weakness [57]. Within 5 years, in patients

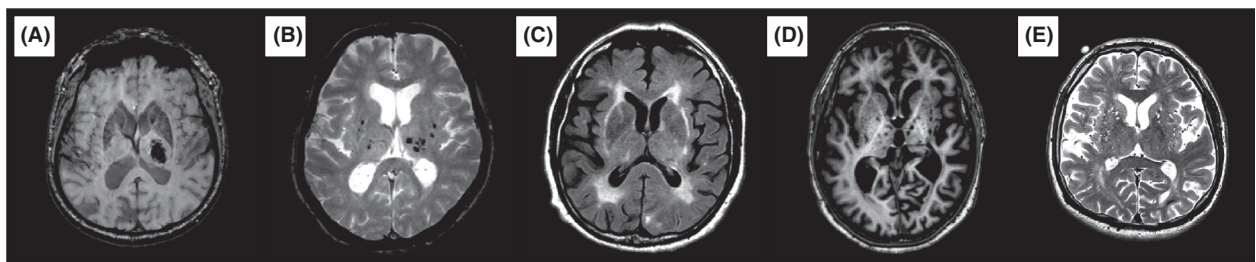


Figure 2. MRI markers of deep perforator arteriopathy. (A) Deep intracerebral haemorrhage. (B) Deep microhaemorrhages. (C) Peribasal ganglia white matter hyperintensities (WMH). (D) Deep lacunes. (E) Basalganglia perivascular spaces (PVS). A–B, T2*-weighted gradient recalled echo (T2*-GRE) MRI sequences; C, fluid-attenuated inversion recovery (FLAIR) MRI sequence; D, T1-weighted MRI image; E, T2-weighted MRI image. A, E, 3T MRI; B–D, 1.5T MRI.

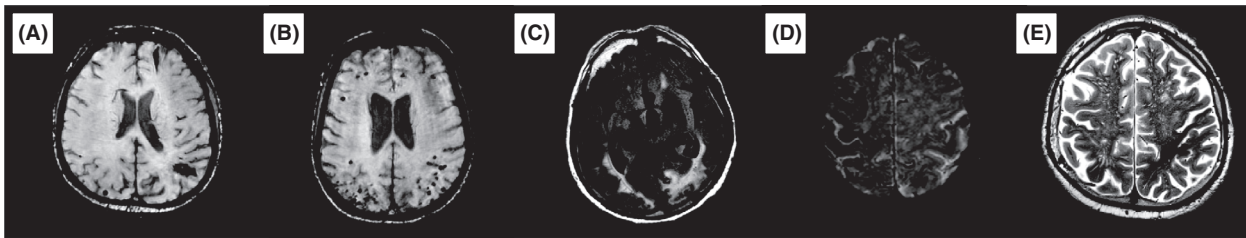


Figure 3. MRI markers of CAA. (A) Cortical intracerebral haemorrhages. (B) Cortical and cortico-subcortical microhaemorrhages. (C) Posterior white matter hyperintensities (WMH). (D) Cortical superficial siderosis (cSS). (E) White matter perivascular spaces (PVS). (A, B, D) T2*-weighted gradient recalled echo (T2*-GRE) MRI sequences; (C) fluid-attenuated inversion recovery (FLAIR) MRI sequence; (E) T2-weighted MRI image. (A, B, E) 3T MRI; (C, D) 1.5T MRI.

with probable CAA and cSS compared to probable CAA without cSS, symptomatic ICH risk was around threefold higher [62].

Nonhaemorrhagic CSVD biomarkers

Recent small (subcortical) infarcts, lacunes of presumed vascular origin and microinfarcts Recent small (subcortical) infarcts and (deep) lacunes are considered to result from CSVD of the deep thalamoperforant, lenticulostriate or pontine paramedian arterioles [63]. Recent small (subcortical) infarcts of the basal ganglia, thalamus, pons, internal capsule or corona radiata cover the approximate territory of a single perforating arteriole. They shrink to either leave a deep lacune, a small lesion of similar signal characteristics to WMH, a CMB or disappear [5].

Lacunae are small fluid-filled cavities located in the deep grey (basal ganglia, thalamus, pons) or white matter (internal or external capsule) (Figure 2D), or display a lobar pattern (centrum semiovale (CSO), frontal, parietal, insular/subinsular, temporal or occipital lobes), and occur within, in contact and at the edge of WMH [64,65]. Deep lacunae result from recent small subcortical infarcts, larger subcortical (striatocapsular) infarcts – both of which are due to lipohyalinosis, or atheromatous or embolic occlusion of a penetrating vessel [66] – or from small deep haemorrhages [22]. Recent small subcortical infarcts and multiple (deep) lacunae have been deemed to be a typical feature of spontaneous DPA [9]. Recent studies, however, suggested there to be an additional association between lobar lacunae and CAA-related haemorrhages [64].

Cortical small DWI hyperintense lesions and microinfarcts (100 μ m to up to 5 mm; mainly detectable on high-field 7T MRI [26,67]) are further (presumably) nonhaemorrhagic DPA and CAA biomarkers [55].

Microinfarcts are related to worse cognitive function and dementia [26,68].

WMH of presumed vascular origin Structural white matter abnormalities become visible as WMH on proton-density, T2- and FLAIR-weighted images [23]. BBB dysfunction and associated interstitial fluid content increase and impaired oligodendrocyte maturation and myelin repair seem to be pivotal pathological substrates of WMH. WMH are further related to reduced cerebral blood flow and impaired cerebrovascular impairment most likely resulting from viable tissue loss [69]. In DPA, WMH are usually symmetrically distributed in the periventricular and deep cerebral or cerebellar white matter, but also in the deep grey matter (basal ganglia, pons; subcortical hyperintensities) [22]. Sporadic DPA seems to be especially characterized by WMH following the peripheral outline of the basal ganglia (peribasal ganglia WMH [70]) (Figure 2C), and by deep grey matter hyperintensities in the brainstem [52]. Conversely, CAA-related WMH especially affect the posterior (deep) white matter (Figure 3C) and seem to more often occur as multiple subcortical spots [70].

Perivascular spaces Perivascular spaces (PVS) are fluid-filled spaces surrounded by leptomeningeal sheets following the typical course of small vessels as they penetrate the grey or white matter; they are the main drainage conduits to remove ‘waste’ out of the brain [22]. On all MRI sequences, PVS have signal intensities similar to cerebrospinal fluid (CSF) [22]. While DPA seems to be preferentially associated with high numbers of basal ganglia PVS (Figure 2E), CAA seems to be related to high numbers of PVS in the hemispheric white matter (especially in the CSO) (Figure 3E) [37,71].

Scoring the total CSVD burden

It has been suggested that there is a need for the standardized quantification of 'total CSVD burden', both pathologically and radiologically, especially in the light of increasing multicentre and meta-cohort studies aiming to understand the contribution of CSVD load to healthcare and socioeconomic costs [72]. Until recently there was a lack of widely accepted and commonly used protocols to quantify and interpret CSVD burden, making it difficult to compare various findings between different centres.

Recent studies tried to overcome those deficiencies by suggesting uniform criteria for the quantification of CSVD load in autopsy and MRI studies. A consensus group developed standardized neuropathological criteria providing pathology-based consensus definitions of how to outline CSVD-related wall alterations of capillaries, small meningeal, cortical, subcortical vessels, such as arteriosclerosis or 'double barrelling' (concentric vessel wall splitting in CAA), or parenchymal pathologies arising from vascular disease (microinfarcts, lacunar infarcts and microhaemorrhages) [73].

Others have proposed scores to quantify the MRI-derived CSVD load in a comparable semiquantitative manner [74–76] in which DPA has been related to deep lacunes, deep/mixed CMB, Bg PVS, deep/periventricular WMH, while CAA has been related to strictly lobar CMB, cSS, CSO PVS, WMH. However, DPA markers are not likely to be specific, though pathological validation is limited. Rating scales including The Cerebral Haemorrhage Anatomical Rating Instrument has been developed to reliably classify ICH locations (lobar, non-lobar, uncertain) using CT and MR scans [77].

The overall implementation of the neuropathological and MRI-based scoring systems should improve the data comparability between different cohorts and centres. Statistically, it should be of advantage not only to use an ordinal scaling approach (which loses some of the available data) but also use continuous measures of CSVD pathology to avoid data information loss.

Detecting DPA and CAA using PET

Using amyloid PET, cerebral A β is detectable *in vivo*. Postmortem studies have shown that A β -PET tracers mainly label insoluble fibrillar (compact/cored) plaques immunoreactive to either A β 42 or A β 40, comprising neuritic A β plaques, while amorphous or diffuse A β

plaques are nearly not detectable [78,79]. Furthermore, quantitative and semiquantitative assessment of A β burden using PET correlates well with the postmortem A β load in the brain [79,80]. As vascular A β deposits are, however, labelled as well, direct *in vivo* differentiation between CAA and other kinds of amyloid deposits using PET is currently impossible [49,81,82].

One recent meta-analysis took into account seven A β -PET studies with an overall number of 106 nondemented CAA patients with symptomatic lobar ICH or clinical presentations associated with CAA (e.g. seizures), 46 nondemented DPA patients with symptomatic deep ICH and 72 patients with Alzheimer's dementia (AD) [83]. On a group level, CAA could be discriminated from DPA by a significantly higher global β -amyloid distribution volume ratio (DVR). From AD, CAA could be differentiated by a significantly lower global DVR and a significantly greater occipital-to-global DVR, supporting the occipital dominance of CAA-related A β retention and suggesting the occipital-to-global A β -ratio as a molecular signature of CAA vs. AD [83].

It is important to note that these findings were derived from a limited number of studies with small sample sizes of selected CAA patients without dementia with otherwise heterogeneous clinical presentations. The analysis also reflects the limited availability of systematic A β -PET studies/data in CSVD, which may also rely on the difficulty of performing molecular imaging in patients with CSVD-related ICH. Notably, one of the recent A β -PET papers, which reported the flow of participants, showed that only 11% of the ICH patients were included in the study [81]. One can overall state that A β -PET currently has a very limited role for CAA diagnosis. Further confirmation and validation of the demonstrated findings and ongoing active research that focusses on molecular tracers specific for vascular amyloid is needed. However, it is not only important to identify biomarkers which are specific for CAA (and CSVD) but also ones which are widely applicable to that population of interest.

Similarities between DPA and CAA

Albeit often considered separately, DPA and CAA share several similarities. These include joint risk factors, arteriolar functional impairment with cerebral blood flow (CBF) reduction, and final brain injury pathways characterized by microstructural white matter changes, global network

disturbances and neurodegeneration which contribute to cognitive profiles of vascular cognitive impairment (VCI) found in both CSVD variants [61,84].

Although age is the most common risk factor for sporadic CSVD both DPA and CAA are further vulnerable to the presence of aHTN, to the intake of oral anti-coagulants and, most likely, to intravenous thrombolysis. That vulnerability includes an associated increased risk of cerebral bleeding, which is not remarkable, as both CSVD variants show similar abnormal vessel wall weakness (tunica media degeneration, BBB damage, microaneurysm formation) prone to leakage and rupture. On the other hand, there are also DPA- and CAA-related small vessel wall thickening, luminal narrowing and occlusions revealing the pathophysiological basis for additional autoregulatory disturbances, CBF reduction and hypoperfusion [85] with the latter commonly associated with CMB and WMH burden [86,87]. However, thus far it seems poorly understood whether there are disease specific CBF alteration patterns preferentially related to DPA or CAA [88].

Small vessel wall disintegration and impaired cerebrovascular haemodynamics may in sum contribute to several downstream pathologies, such as diffusion tensor imaging-related microstructural white matter alterations [89], as well as to overall brain network disturbances. In CAA, microstructural white matter damage seems to affect the temporal lobe [90], while in DPA it is found more extensively (internal/external capsule, periventricular frontal white matter) [91]. In CAA, brain network alterations are predominantly found in the occipital and posterior temporal lobes progressing over the course of time [92], while in DPA frontal and lateral temporal networks seem to be rather affected [93]. Microstructural white matter integrity is further influenced by APOE ϵ 4 carriage and aHTN [94], and interactions between those factors and CSVD burden have thus to be taken into account.

Neurodegeneration (diffuse cortical and subcortical grey matter atrophy, parieto-temporal glucose hypometabolism) is another finding reported in sporadic CSVD [95,96]. DPA- as well as CAA-related neurodegeneration seems thereby to be quite widespread (in frontal, temporal, occipital, insular, hippocampal regions) [92,95,97,98]. One latest study additionally reported an association between greater progressive posterior white matter connectivity loss and greater progression of occipital cortical thinning [92]. Indeed, results on

CSVD neurodegeneration patterns are inhomogeneous, demanding for the disentanglement of the additional impact of concomitant neurodegenerative disorders as a concurrent source of cortical alterations [95].

Both DPA and CAA are the major sources of VCI and vascular dementia [22,99], with a cumulative dementia incidence of around 70% after 5 years for CAA patients [100]. Around one of three of the DPA and CAA subjects seem to reveal VCI, with disturbed executive function and reduced processing speed as well as CAA-related visuo-perceptual impairment being the most consistent findings [101–103]. This is not surprising, given the supposed relationship between CSVD and several diverse structural and functional pathologies (see above). Indeed, apart (and independently) from those downstream pathologies CSVD-linked non-haemorrhagic and haemorrhagic biomarkers (e.g. WMH, CMB, lacunes, microinfarcts), are themselves associated with cognitive decline [104,105].

Common occurrence of DPA and CAA in the ageing brain and dementia – evidence from autopsy and imaging studies

The majority of neuropathology studies have focused either on (i) the description of the extent of hypertensive CSVD pathologies (e.g. lacunes), (ii) CAA severity assessment (especially in AD patients) or (iii) the evaluation of general DPA and CAA frequencies in the ageing brain, while only few human autopsy studies give more precise overlap prevalence of the two CSVD entities. In this instance, Ritter *et al.* described a weak relationship between deep haemorrhages and CAA with 18% of the patients showing that constellation [106]. Multiple vascular diseases were found in 7%–26% of population samples of the nondemented elderly [107,108]. One recent autopsy study identified much higher overlap prevalences with 39 of 52 (75%) patients with pathologically defined CAA displayed DPA-related arteriolosclerosis [74]. Another post-mortem study showed that isolated CAA was rare in lobar ICH (16%), but commonly occurred together with other small vessel disease (81%) [38].

Similarly, there are nearly no consistent estimates of the overlap between DPA- and CAA-related pathologies on neuroimaging. Two studies reported on mixed patterns of DPA and CAA (lobar ICH and deep microbleeds (MB) or deep ICH and lobar MB or lobar ICH and deep

ICH) in 19% to 23% of the cases [52,109]. Autopsy of one of those patients with lobar ICH and deep MB revealed severe cortical CAA together with severe white matter arteriosclerosis [52].

To more systematically investigate the *in vivo* prevalence of the overlap between DPA- and CAA-related MRI features we conducted a systematic literature search in PubMed. We thereby focused on papers published in English between 1 Jan 2008 and 6 June 2017. The search terms ‘microbleeds’, ‘perivascular spaces’, ‘amyloid PET’, ‘white matter hyperintensities’ and ‘cortical superficial siderosis’ were used alone or in combination with each other. Papers taking account of MRI studies identified through these searches were selected and evaluated in terms of the *in vivo* frequencies of DPA and CAA MRI marker prevalence. We thereby consider DPA to be related to strictly deep haemorrhages (CMB, ICH), deep lacunes and (severe) deep PVS, while CAA is defined by the modified Boston criteria comprising strictly lobar haemorrhages (CMB, ICH) and cSS. We also included severe CSO PVS as a more recent proposed marker of CAA [18,37,110]. To identify the *in vivo* prevalence of overlapping DPA- and CAA-related pathologies we focused on the reported frequencies of (i) DPA-suspected MRI features in subjects diagnosed to suffer from CAA based on the modified Boston criteria; (ii) CAA-related MRI features in subjects suspected to suffer from DPA based on haemorrhagic MRI features (deep ICH/deep CMB) and (iii) MRI features suspected to be related to DPA and CAA in aged, cognitively impaired or demented cohorts (Table 1). Estimation of the overlapping prevalence of DPA- and CAA-related pathologies was based on the acquisition of the joint frequencies of at least one DPA-related MRI feature (deep CMB, or deep ICH, or deep lacunes, or severe deep PVS) together with at least one CAA-related MRI feature (lobar CMB, or lobar ICH, or cSS, or severe CSO PVS) (Table 1).

In CAA, the prevalence of cases revealing MRI features suspected to be related to DPA ranges between 7% and 30% (Table 1, violet); in various stroke cohorts comprising patients with transient ischaemic attack, ischaemic stroke or ICH the overlap prevalence between DPA and CAA ranges between 2% and 68% (Table 1, yellow); in cognitively impaired subjects prevalence ranges between 9% and 33% (Table 1, green), while in the community-based population overlap frequencies range from 1% to 10% (Table 1, blue).

Our data should be considered with caution as there is little validation of the proposed MRI markers’ sensitivity and specificity to indicate DPA in the absence of CAA, and vice versa. Similarly, we cannot reliably assume that a mixture of patterns reflects an overlap between the two CSVD entities. For example, mixed CMB patterns could be due to a co-occurrence of DPA and CAA but might also denote severe and widespread DPA (see above). Our analysis should be considered as hypothesis generating. We hope that it might support future studies combining autopsy and imaging data to gain deeper insights into the overlapping frequencies between the two CSVD entities.

Interaction between DPA and CAA – pathophysiological considerations

Throughout life A β is derived from cellular production (e.g. by neurons and oligodendrocytes) by enzymatic cleavage of the transmembrane amyloid precursor protein. The soluble A β protein is eliminated from the brain along the cerebral vascular system by enzymatic degradation, pericytic internalization, transport across the BBB and brain-wide lymphatic A β drainage to the extracranial lymphatic system within (a) the interstitial fluid (ISF) bulk flow along the vessels’ BM or (b) along glial water channels of the glymphatic system [111,112]. All of those mechanisms could indicate key links connecting DPA and CAA. Specifically, the mechanisms eliminating A β out of the brain depend on the integrity of cerebral microvessels, with the latter failing with age, high vascular risk and vessel wall damage [112]. In the following section, we briefly introduce the vascular mechanisms that are involved in the A β elimination from the brain to discuss how those pathways could contribute to the pathophysiological interplay between DPA and CAA.

Physiological A β clearance

Extracellular A β can be degraded enzymatically in the cells of the neurovascular unit (NVU), for example, microglia, astrocytes, and vascular smooth muscle cells (Figure 4, physiological A β elimination) [112,113]; and pericytes internalize and clear A β aggregates as well [114].

Interstitial A β can also be transferred into the blood, and vice versa, from the blood into the brain. Clearance

Table 1. Estimated overlap of DPA and CAA MRI features

Reference	Cohort	Demographics	Imaging sequences (FS/ET/ST)	Microbleeds (CMB)	Perivascular spaces (PVS)	Mixed CAA and DPA markers	Prevalence of likely overlap between CAA and DPA*
Schreiber <i>et al.</i> , unpublished data [#]	Magdeburg hospital-based small vessel disease cohort, N = 183, selection through the detectability of lobar and/or deep ICH and/or CMB	Age 76.8, 50% male, 93% aHTN	T2*-GRE (1.5–3 T/16–18 ms/3.3–5 mm)	7% with mixed CMB	32% severe CSO PVS in deep CMB	31% deep CMB in lobar ICH; 33% deep CMB with lobar lacunes	7%–33%
Pasi <i>et al.</i> , Neurology 2017; Charidimou <i>et al.</i> , Neurology 2016 & 2017; Smith <i>et al.</i> , Stroke 2010	Massachusetts General Hospital (MGH), Boston, USA, N = 316–456, symptomatic ICH (60%–70% lobar, 30%–0% deep)	Age 71.4–71.9, 52%–3% male, 71%–3% aHTN, 21%–8% APOEε4+, 11%–4% APOEε2+	T2*-GRE (1–1.5 T/15–70 ms/1–8 mm)	16% with mixed CMB	15%–8% severe CSO PVS in deep ICH; 3%–% severe BG PVS in lobar ICH	39% deep CMB in lobar ICH; 30% lobar CMB in deep ICH; 2% deep lacunes in lobar ICH; 4% deep CMB & 5% severe BG PVS in patients with severe CSO PVS; 36% lobar CMB & 11% cSS in patients with severe BG PVS	2%–9%
Boulois <i>et al.</i> , 2017 Neurology	MGH, N = 261, probable CAA without ICH, 35% TFNES, 65% cognitive symptoms	Age 75.8, 60% male, 66% aHTN	T2*-GRE (1.5 T/50 ms/5 mm)	No separate consideration of deep and lobar CMB	7% severe BG PVS	30% with deep, subcortical or pontine lacunes	7%–0%
Doi <i>et al.</i> , 2015, Intern Med	Hiroshima Red-Cross Hospital and Atomic-Bomb Survivors Hospital, Hiroshima, Japan, N = 122, 15% SCI, 11% MCI, 59% AD, 7% VaD, 2% LBD, 4% others	Age 78.8, 39% male	T2*-GRE (1.5 T/17 ms/5 mm)	10% with mixed CMB	Na	na	10%
Na <i>et al.</i> , 2015, Neurology	Samsung Medical Center, Seoul, South Korea, N = 232, 39% AD, 61% VaD	Age 72.2, 42% male, 63% aHTN, 37% APOEε4+, 10% APOEε2+	T2*-GRE (1.5 T/7 ms/5 mm)	No separate consideration of deep and mixed CMB	Na	17% mixed or deep CMB in patients with cSS	17%
Meier <i>et al.</i> , 2014, Cerebrovasc Dis	Manhattan, New York, USA, N = 203, community-based ageing study	Age 84.2, 32% male, 68% aHTN	T2*-GRE (1.5 T/31 ms/2 mm)	3% with mixed CMB	Na	na	3%
Romero <i>et al.</i> , 2014, Stroke	Framingham Original and Offspring cohort participants, Mass, USA, N = 1965	Age 67.2, 46% male, 56% aHTN, 23% APOEε4+	T2*-GRE (1.5 T/26 ms/5 mm)	3% with mixed CMB	Na	na	3%

Table 1. (Continued)

Reference	Cohort	Demographics	Imaging sequences (FS/ET/ST)	Microbleeds (CMB)	Perivascular spaces (PVS)	Mixed CAA and DPA markers	Prevalence of likely overlap between CAA and DPA*
Wiegman <i>et al.</i> , 2014, J Neurol Sci	Washington Height/Inwood Columbia Aging Project (WHICAP), Manhattan, USA, N = 243	Age 84.5, 30% male, 38% aHTN, 27% APOEε4+, 18% APOEε2+	T2*-GRE (1.5 T/31 ms/2 mm)	5% with mixed CMB	Na	Na	5%
Yakushiji <i>et al.</i> , 2014, Neurology	Kashima Scan Study, Saga University Faculty of Medicine and Yuai-Kai Oda Hospital, Saga, Japan, N = 1575	Age 57.1, 47% male, 35% aHTN	T2*-GRE (1.5 T/31 ms/2 mm)	1% with mixed CMB	Na	9% deep/infratentorial CMB & 10% lacunes in patients with severe CSO PVS; 5% lobar CMB in patients with severe BG PVS	1%–0%
Charidimou <i>et al.</i> , 2013, J Neurol Neurosurg Psychiatry	University College London Hospitals, London, UK; Cliniques Universitaires Saint Luc Brussels, Belgium; CHU Mont-Godinne UCL Belgium; Addenbrooke's Hospital Cambridge, UK, N = 121, spontaneous ICH (63% lobar, 37% deep or mixed)	Age 69.4, 57% male, 73% aHTN	T2*-GRE (1.5 T/15–70 ms/4–6 mm)	Mixed CMB na	58% severe CSO PVS in deep/mixed ICH; 4% severe BG PVS in lobar ICH	68% lobar CMB in deep/mixed ICH	4%–8%
Gregoire <i>et al.</i> , 2013, Stroke	National Hospital for Neurology and Neurosurgery, London, UK, N = 320, 79% ischaemic stroke, 21% TIA	Age 63.9, 59% male, 74% aHTN	T2*-GRE (1.5 T/40 ms/5 mm)	8% with mixed CMB	na	na	8%
Martinez-Ramirez <i>et al.</i> , 2013, Neurology	Massachusetts Alzheimer's Disease Research Center (ADRC), Boston, USA, N = 89, 58% MCI, 42% dementia	Age 72.7, 43% male, 49% aHTN	SWI (3 T/21 ms/1.2 mm)	No separate consideration of deep and mixed CMB	Na	9% lacunes in patients with severe CSO PVS; 33% lobar CMB in patients with severe BG PVS	9%–3%
This <i>et al.</i> , 2010, Stroke	Stroke Unit of the University Hospitals in Leuven, Belgium, N = 487, ischaemic stroke or TIA	Age 72, 60% male, 64% aHTN	T2*-GRE (1–3 T/26–35 ms/7 mm)	9% with mixed MB	Na	na	9%
Goos <i>et al.</i> , 2009, Stroke	VU University Medical Center Amsterdam, Memory Clinic, Amsterdam, The Netherlands, N = 63, AD	Age 72.5, 63% male, 35% aHTN, 71% APOEε4+	T2*-GRE (1–1.5 T/26–35 ms/5 mm)	16% with mixed CMB	Na	na	16%

Table 1. (Continued)

Reference	Cohort	Demographics	Imaging sequences (FS/ET/ST)	Microbleeds (CMB)	Perivascular spaces (PVS)	Mixed CAA and DPA markers	Prevalence of likely overlap between CAA and DPA*
Soo <i>et al.</i> , 2008, J Neurol	Regional Hospital, Hong Kong, China, N = 908, ICH	Age 69.3, 58% male, 68% aHTN	T2*-GRE (1.5 T/ 30 ms/5 mm)	10% with mixed CMB	Na	na	10%
Vernooij <i>et al.</i> , 2008, Neurology	Population-based Rotterdam Study, Rotterdam, The Netherlands, N = 1062	Age 69.6, 49% male, 71% aHTN, 27% APOEε4+, 16% APOEε2+	3D T2*-GRE (1.5 T/ 31 ms/1.6 mm)	5% with mixed CMB	Na	na	5%

*Estimation of overlap prevalences of DPA- and CAA-related MRI features (farthest right column) is based on the frequencies of the joint occurrence of at least one DPA-related MRI feature together with at least one CAA-related MRI feature as given in the constellations presented in the columns 3, 4 and 5. Abbreviations: AD, Alzheimer's Disease; aHTN, arterial Hypertension; APOE, Apolipoprotein E; BG, basal ganglia; CAA, cerebral amyloid angiopathy; CSO, centrum semiovale; cSS, cortical superficial siderosis; CMB, cerebral microbleeds; ET, MRI echo time; FS, MRI field strength; GRE, Gradient-recalled echo; ICH, intracerebral haemorrhage; LBD, Lewy body dementia; MCI, mild cognitive impairment; N, number of patients/participants; na, not available; PVS, perivascular spaces; SCI, subjective cognitive impairment; ST, MRI slice thickness; TFNEs, transient focal neurological episodes; TIA, transient ischaemic attack; VaD, vascular dementia; mean age is given; violet, CAA cohorts; yellow, stroke cohorts; green, cognitively impaired patients; blue, community-based cohorts; # our own cohort consists of patients suffering from mixed diagnoses (65% ischaemic or haemorrhagic stroke, 10% cognitive decline/dementia or 25% incident CMB), and thus, results are not shaded with any of the colours introduced above.

from the parenchyma into the blood occurs directly at the BBB, for example, through specific transport mechanisms located in the endothelium and the glia limitans (astroglial endfeet processes surrounding the BBB) [112]. While interstitial A β can pass freely through the glia limitans, its endothelial clearance into the blood has to take place via specialized transporters (e.g. low-density lipoprotein receptor-related protein (LRP), ATP-binding cassette transporters) [112,115]. Pericyte-related A β clearance seems further to rely on LRP1–APOE interactions [114]. Plasma A β can also be transported into the interstitium via soluble transporters such as soluble advanced glycosylation end product-specific receptor, while soluble low-density lipoprotein receptor-related protein binds the circulating A β to prevent free A β access to the brain (Figure 4, physiological A β elimination) [112,115].

Soluble A β additionally passes through the cortical and deep grey matter interstitial space [116] to be then cleared out of the brain along the BM route [116] or along the glymphatic system [111,117]. Motive forces of BM-associated A β drainage is related to the directional ISF movement through the arterial pulse wave ([118,119]) and ISF solutes are cleared along the artery walls' BM in the opposite direction to the arterial blood flow (Figure 4, physiological A β elimination) [120,121].

Failure of the A β clearance system through age, vascular risk factors and genetics

There is a triumvirate comprising age, vascular risk factors and genetics, which together are related to NVU and small vessel wall alterations which in turn seem to be the pivotal issues impairing A β elimination from the brain (Figure 4).

First, age itself has several detrimental effects on different aspects of the A β clearance pathways: BBB integrity impairment, endothelial LRP1 expression decrease, BM-associated A β drainage reduction by (i) decreasing certain BM proteins, promoting (ii) the loss of smooth muscle cells and (iii) vessel wall stiffening as a result of generalized intima thickening and tunica media fibrosis (Figure 4) [115,122,123].

Second, A β elimination is disturbed by vascular risk factors. Hyperinsulinaemia impairs enzymatic A β degradation in a way that insulin and A β compete for enzymatic clearance by the insulin-degrading enzyme.

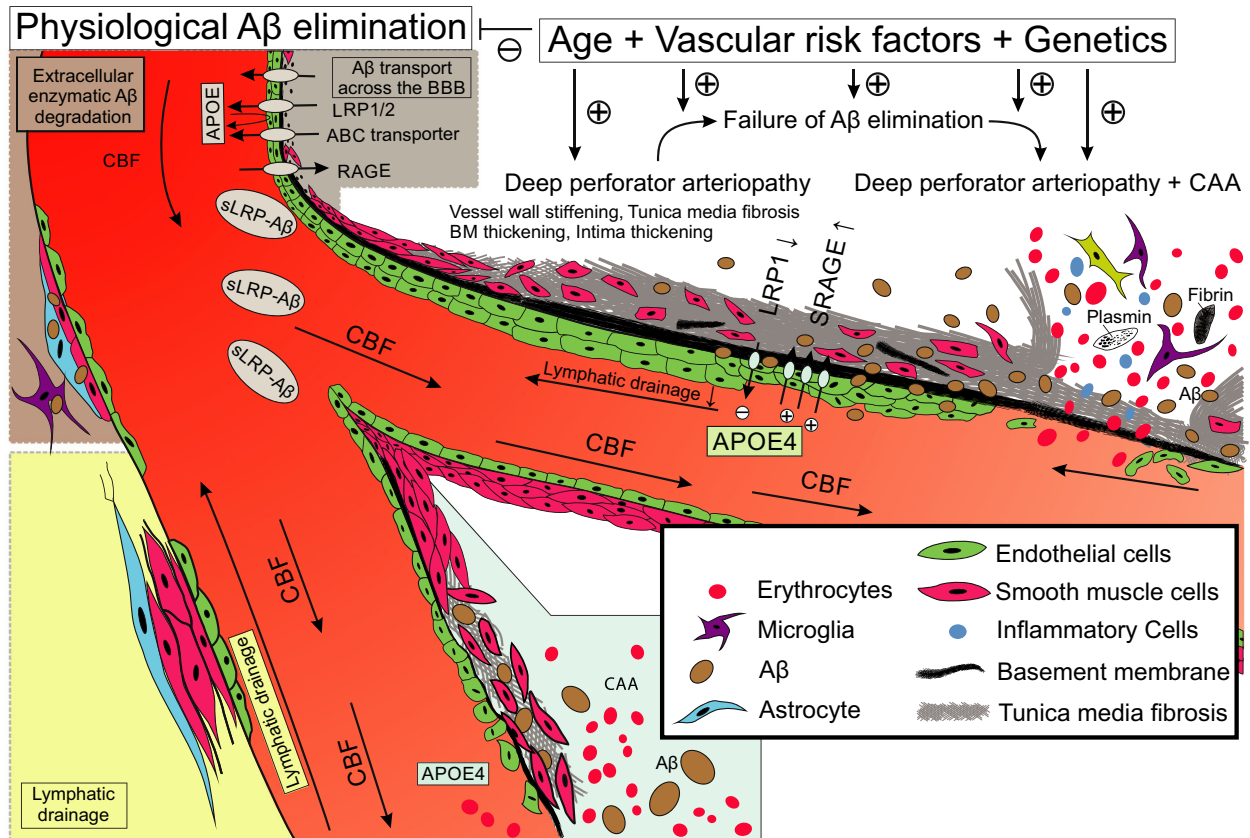


Figure 4. Interaction between deep perforator arteriopathy and cerebral amyloid angiopathy. The left part of the figure demonstrates the physiological elimination of the soluble β -amyloid (A β) protein along the cerebral vascular system. This includes: (i) enzymatic degradation through various enzymes localized within microglia, astrocytes and smooth muscle cells, (ii) transport across the blood-brain barrier (BBB) or within the circulation via specialized transporters and (iii) lymphatic A β drainage to the extracranial lymphatic system along the arteries' basement membranes into the opposite direction to the arterial blood flow (CBF). Age together with vascular risk factors (such as arterial hypertension, diabetes [and hyperinsulinaemia] or hyperlipidaemia) and Apolipoprotein E (APOE) 4 positivity not only detrimentally affect all aspects of the A β clearance pathways, but also lead to small vessel wall remodelling comprising, for example, endothelial damage, BBB breakdown, tunica media and basement membrane thickening, as well as associated stiffening/reduced arterial pulsation as found in, for example, deep perforator arteriopathy. The latter in turn further impairs vascular A β drainage mechanisms overall creating a state prone to cerebral amyloid angiopathy (CAA) development. Vascular A β itself impairs vascular autoregulation and BBB integrity promoting further vessel wall damage (comparable to that found in deep perforator arteriopathy). Deep perforator arteriopathy and CAA within the same vessel segments should then even potentiate small vessel wall damage resulting in an inflammatory-haemorrhagic-thrombotic state forwarding neurodegeneration and cognitive decline. ABC transporter, ATP-binding cassette transporter; LRP, low-density lipoprotein receptor-related protein; sLRP-A β , low-density lipoprotein receptor-related protein A β complex; sRAGE, soluble advanced glycosylation end product-specific receptor.

Diabetes mellitus suppresses the clearance of ISF, and chronic aHTN seems to activate brain vascular RAGE favouring the parenchymal A β uptake. Moreover, a lifelong high-fat diet and hyperlipidaemia impair lymphatic BM A β drainage (Figure 4) [124–126].

Considering genetic aspects, the APOE ϵ 4 isoform is less efficient compared to, for example, the APOE ϵ 3 or APOE ϵ 2 variant at mediating the A β elimination. Binding of A β to APOE ϵ 4 redirects its rapid clearance from LRP1 to the very low-density lipoprotein receptor,

which internalizes A β /A β -APOE ϵ 4 complexes more slowly [127]. APOE ϵ 4 moreover reduces the A β efflux across the BBB through the APOE ϵ 4's pro-inflammatory properties (leading to BBB/NVU damage), APOE ϵ 4-related LRP1 lowering while increasing RAGE levels or through APOE ϵ 4 positivity-related BM alterations (Figure 4) [115,128–132].

Cerebral haemorrhage, embolic stroke and microinfarcts themselves additionally cause widespread inhibition of glymphatic pathways [133,134]. It is, indeed,

very conceivable that there is an interaction between age, vascular risk, genetics and CSVD-related cerebrovascular injury on the A β clearance pathways.

Interaction between DPA and CAA – how can we move forward using biomarkers?

CSVD comprising NVU damage, vessel wall stiffening and reduced arterial pulsation virtually affects all pathways and mechanisms involved in the vascular A β clearance from the brain. Besides CSVD itself, its risk factors (age, vascular disease and genetics) additionally have detrimental effects on the A β transport mechanisms. Moreover, a vicious circle with small vessel wall damage mediating the effect of risk profile on A β clearance failure has also to be considered.

By this means, it seems logical that small vessel wall damage (as typically occurs in DPA) could predict CAA development [135,136]. For instance, CAA-related increase in CSO PVS and WMH could just indicate small vessel wall damage, BBB breakdown and fluid stagnation with impeded A β clearance along the long penetrators of the superficial perforating small arteries and arterioles supplying the white matter ('medullary branches'), commonly affected by DPA in the ageing brain [137]. Vice versa, once CAA has developed vascular A β (which is vasoactive) promotes disturbances of endothelial properties resulting in a failure of vascular autoregulation and BBB leakage [138]. In the first instance, increased vascular A β thereby further impairs solute clearance and endothelial protein transport, facilitating the accumulation of potentially toxic products and its accompanying local inflammation in the small vessel walls. The latter promotes ongoing NVU damage, endothelial failure and finally small vessel wall reorganization, as it is typically found in DPA (Figure 4). There are few experimental studies reporting pericyte loss in CAA and CAA development in the face of microvascular BBB breakdown [14,139,140], supporting the hypothesized relationship between small vessel wall damage and impaired vascular A β clearance. Further studies that decidedly focus on the A β clearance in DPA are needed.

One may argue that the more subcortical distribution of DPA does not accommodate its supposed CAA promoting effect. This point of view mainly stems from autopsy studies relating DPA features (arteriosclerosis, lacunes) to deep grey matter structures. However,

DPA as defined by neuropathological criteria displays advanced and end-stage disease. By now, there is quite common acceptance that DPA is initiated by endothelial damage and BBB breakdown [11–14], which so far is in general not considered when investigating human autopsy tissue. In DPA animal models, BBB integrity loss is commonly found in the same cortical areas affected by CAA [141,142]. Furthermore, its association with cortical atrophy and cortical microinfarcts (see above) supports the idea that DPA is a mixed cortical-subcortical instead of a pure subcortical condition.

If we aim to investigate the hypothesis that there is an interaction between DPA and CAA augmenting each of the two CSVD variants, there is a need to detect and quantify the integrity of the A β drainage pathways' on a translational level. The pathways' integrity needs to be related to DPA and CAA; first warranting the definition of markers that are deemed to be CAA or DPA specific (for CAA: severe CSO PVS, cSS, cortical CMB, occipital A β retention; for DPA: severe Bg PVS, deep lacunes, deep CMB) (see above).

Thus far, most studies have mainly focused on the association between whole-brain A β retention (taking into account either A β PET or CSF A β levels) and CSVD features such as WMH. The majority of those studies found a relationship between cerebral A β load and CSVD marker burden (e.g. [143,144]), while only few failed (e.g. [145]). There is, moreover, evidence, that greater cortical A β retention and more extended CSVD interact to predict cognitive decline and dementia (e.g. [146]). Those data overall so far best support an association and the synergistic interplay between A β and small vessel pathology. However, several studies did not strictly separate between DPA and CAA MRI markers nor was there a particular consideration of the occipital A β load. The specific association between vascular A β and small vessel wall damage has thus not rigorously been taken into account, while instead thus far rather parenchymal A β plaque load has been related to CSVD-associated brain damage.

To better understand the specific interplay between CSVD and the failure of A β drainage *in vivo*, different candidate markers have to be defined. Of course, histopathology is the 'gold standard' to quantify CSVD burden. It is, however, usually available from subjects with evacuation of large intracerebral haematoma or from autopsy data. Human tissue data thus generally reflect end-stage CSVD, impeding the prediction of the

course of disease at its earlier stages. The aim, however, has to be to understand the interactions between CSVD variants at a preclinical stage, comprising the yet absence of cognitive decline and stroke-like symptoms.

Future research needs to show if CSF biomarkers could play a role as well. One recent meta-analysis suggested that CAA is characterized by a CSF pattern, distinct from healthy controls and AD patients, of decreased A β 40 levels with marginally elevated total tau protein [147]. Direct systematic comparisons of CSF biomarkers between DPA and CAA are still missing. While already established as a CSF biomarker in certain neurodegenerative diseases [148], with the exception of one study [149] neurofilament light chain indicating axonal damage and myelin breakdown has thus far, however, not been taken into account in CSVD.

Additionally, there is an imperative need for new markers allowing for visualizing and quantifying endothelial damage and the (g)lymphatic fluid drainage in the human brain to identify patients with an early decline in the A β clearance pathways. The most widely used technique to investigate endothelial and BBB integrity is dynamic contrast-enhanced (ce) MRI with paramagnetic gadolinium-based contrast agents with small molecular weights (e.g. gadolinium with diethylenetriaminepentaacetate) passing the disrupted endothelium. Endothelial permeability indicating BBB integrity (giving a hint for endothelial transporter function) can be assessed by calculating the contrast agents transfer rate from the intravascular into the extravascular space. MRI postprocessing approaches further allow for the visualization of the contrast agent's distribution over time within certain regions of interest or on whole-brain voxel-wise level. A stronger signal enhancement stands for a higher agent concentration within the extravascular space indicating BBB leakage which can be quantified through calculating the leakage rate and volume [150]. Indeed, it is still challenging to detect subtle endothelial dysfunction (as it is found in early DPA stages), but improved MRI methodology is already underway [151]. Recent experimental studies additionally displayed the potential of ce MRI based on the intrathecal injection of a gadolinium derivate with a larger molecular weight (e.g. GadoSpin) to visualize the para/perivascular CSF/ISF flow along brain-wide A β drainage pathways of the small penetrating arteries [152].

Moreover, using 7T high-resolution time-of-flight or ce MR angiography (MRA) there is the chance to directly visualize the small vasculature's lumen and walls (e.g. of the lenticulostriate, white matter, cortical arteries) [153]. That technique together with recent advances in 3D phase contrast MRA and in quantitative susceptibility imaging will guide in the direct visualization of the temporal evolution of (inflammatory) small vessel wall damage, associated blood flow and pulsatility alterations as well as resulting haemorrhages [154,155]. When combining those high-resolution approaches with molecular and ce imaging as well as CSF biomarkers there seems to be a good chance to move forward in the deeper understanding on the causal interaction between the two age-related CSVD entities.

Conclusion and outlook

Based on pathophysiological considerations, shared risk factors and evidence derived from neuroimaging data, we suggest considerable yet understudied overlap and interaction between DPA and CAA. These two common CSVD entities should not be viewed as separate entities but, rather, variants along a continuous age-related CSVD spectrum. Future research has to focus on the profile of patients at higher risk to develop both DPA and CAA. Which type of individual first develops endothelial failure and BBB breakdown to later exhibit A β deposition within the small vessel walls? And, vice versa, what is the phenotype of these patients first displaying tunica media and BM damage with associated CAA development to subsequently reveal DPA features such as BBB breakdown, arteriosclerosis and lacunar infarctions? What is the role of age, genetics and vascular risk factors within that circle? The proposed overlap and interaction between nonamyloid and amyloid vascular pathologies will moreover require new concepts to disentangle how the two CSVD entities together are linked to downstream pathologies such as the accumulation of further misfolded proteins and neurodegenerative processes. We will further have to understand if DPA and CAA act as independent, synergistic or potentiating factors on cognitive decline and stroke development. The idea that DPA could display a risk factor for CAA initiation and aggravation will probably open new and better therapeutic options for amyloid-related vascular pathologies which thus far are still fatal and not treatable conditions.

Author contributions

SS was involved in data analysis, concept and design and drafting the manuscript.

AWN was involved in data analysis.

FS was involved in data analysis, graphics design and data interpretation.

SJ, AA, VS and VP were involved in acquisition of data, data analysis and critical revision of the manuscript for important intellectual content.

CM was involved in acquisition of data and data analysis.

ROC was involved in critical revision of the manuscript for important intellectual content.

DJW was involved in concept and design, drafting the manuscript, critical revision of the manuscript for important intellectual content and study supervision.

Disclosure of conflicts of interest

None of the authors have any conflicts of interest to disclose.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Summary Box

- DPA and CAA share haemorrhagic (ICH, CMB) and nonhaemorrhagic (RSSI, WMH, PVS) MRI markers
- Further similarities between DPA and CAA comprise CBF reduction, microstructural white matter changes, global network disturbances, neurodegeneration and cognitive decline
- Evidence of the common occurrence of DPA and CAA in the ageing brain come from very few autopsy studies (prevalence of common occurrence = up to ~80% in ICH populations)
- Systematic literature search in PubMed considering the in vivo prevalence of the overlap between DPA- and CAA-related MRI features led to the following results

- o overlap prevalence of 7%–30% in CAA defined through the Boston criteria
- o overlap prevalence of 2%–68% in stroke cohorts (including e.g. TIA, ICH)
- o overlap prevalence of 9%–33% in cognitively impaired subjects
- o overlap prevalence of 1%–10% in the community-based population
- We consider DPA and CAA not only to occur together but also to interact with one another
- Interaction takes place through a failure of the A β clearance pathways along the damaged small vessel wall
- New biomarkers are needed to detect early small vessel wall damage and related failure of A β clearance pathways, to identify patients at risk to develop both DPA and CAA

Abbreviations: A β , β -amyloid; CAA, Cerebral amyloid angiopathy; CBF, Cerebral blood flow; CMB, Cerebral microbleeds; DPA, Deep perforator arteriopathy; ICH, Intracerebral haemorrhage; MRI, Magnetic resonance imaging; PVS, Perivascular spaces; RSSI, Recent small subcortical infarcts; TIA, Transient ischaemic attack; WMH, White matter hyperintensities.

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