Neuropathology and Applied Neurobiology (2020), **46**, 219–239 doi: 10.1111/nan.12576

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

S. Schreiber*†‡, A. Wilisch-Neumann*†, F. Schreiber*†, A. Assmann*†, V. Scheumann*, V. Perosa*†, S. Jandke*†, C. Mawrin§, R. O. Carare¶ and D. J. Werring**

**Department of Neurology, Otto-von-Guericke University, Magdeburg, Germany, †German Center for Neurodegenerative Diseases (DZNE) within the Helmholtz Association, Magdeburg, Germany, ‡Center for behavioral brain sciences (CBBS), Magdeburg, Germany, §Department of Neuropathology, Otto-von-Guericke University, Magdeburg, Germany, ¶Faculty of Medicine, University of Southampton, Southampton, UK and **Stroke Research Centre, Department of Brain Repair & Rehabilitation, UCL Institute of Neurology, The National Hospital for Neurology and Neurosurgery, London, UK*

Schreiber S, Wilisch-Neumann A, Schreiber F, et al. (2020) *Neuropathology and Applied Neurobiology* **46**, 219–239
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, intracebral 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 (Aβ) 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

Correspondence: Stefanie Schreiber, Department of Neurology, Otto-von-Guericke University, Leipziger Straße 44, 39120 Magdeburg, Germany. Tel: +49 391 6713431; Fax:+ 49 391 6715233; E-mail: stefanie.schreiber@med.ovgu.de

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 arteriolosclerosis, fibrinoid necrosis and lipohyalinosis (Figure 1**A**), 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 β40 (Aβ40) protein (and, to a lesser extent, Aβ42): (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 1**B,C**) [17]. Vascular Aβ 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 Aβ, which compared to noninflammatory sporadic CAA displays more widespread MRI pathologies (WMH, CMB) and lymphocytes/macrophages within/surrounding the Aβ-laden vessels (Figure 1**G–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 nonhaemorrhagic 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

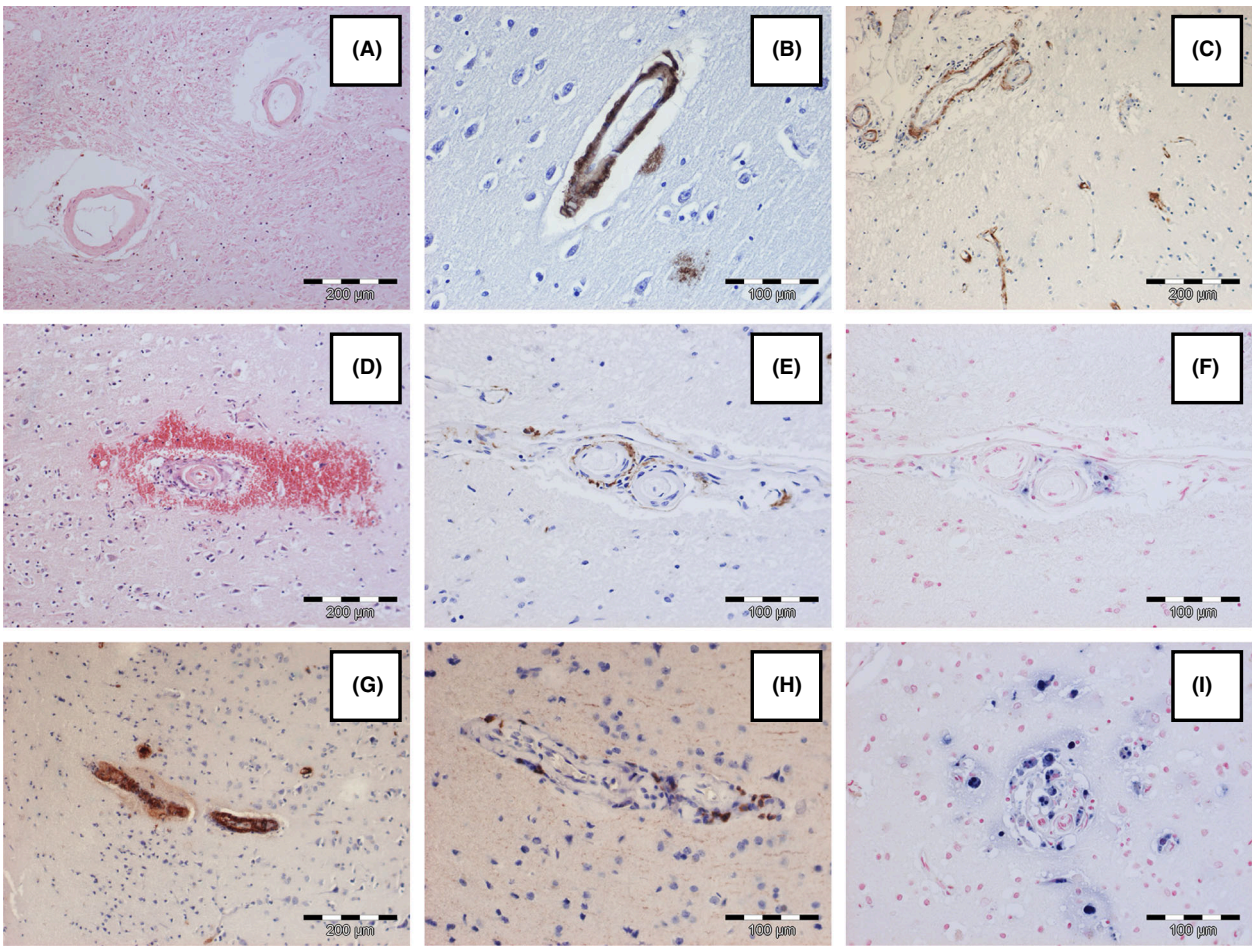

Figure 1. Microscopic features of small vessel disorders in autopsy brain tissue. (**A**) Deep perforator arteriopathy with thickening of the small blood vessels and enlargement of perivascular spaces (H&E stain). (**B**) Cerebral amyloid angiopathy (CAA) is characterized by the deposition of ß-amyloid (Aß) in the walls of small blood vessels. Aß deposition is also seen in small plaques (ß-amyloid immunostaining). (**C**) CAA affects several leptomeningeal (upper left part) and small parenchymal cortical blood vessels (ß-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, ß-amyloid deposition (**E**) and old haemorrhages with haemosiderin deposition around the blood vessels (**F** iron staining). (**G–I**) CAA-related inflammation (CAA-ri) with Aß 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 (APOEε2 or APOEε4 allele carriage) [29,30]. APOEε2 status has thereby been associated with CAA-type 2 and a haemorrhagic CAA phenotype, while APOEε4 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 2**A**), 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 3**A**), 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 1**D**–**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 2**B**) [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 3**B**) [47,48]. The burden of CAA-related lobar CMB seems to be associated with cortical position emission tomography (PET) Aβ load [49,50], but a recent analysis questioned the common expectation that in CAA, the ruptured vessel displays significant Aβ load, as microhaemorrhages were preferentially found surrounding the Aβ 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 3**D**) 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

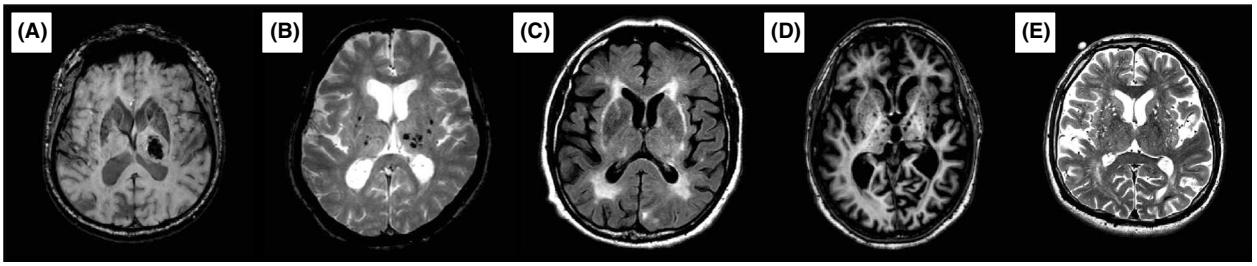

Figure 2. MRI markers of deep perforator arteriopathy. (**A**) Deep intracerebral haemorrhage. (**B**) Deep microhaemorrhages. (**C**) Peri-basalganglia white matter hyperintensities (WMH). (**D**) Deep lacunes. (**E**) Basalganglia perivascular spaces (PVS). A</B>, **B**, T2*-weighted gradient recalled 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.

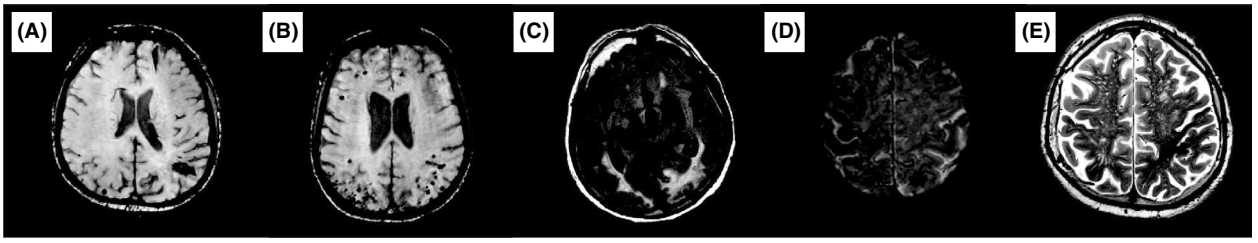

Figure 3. MRI markers of CAA. (**A**) Cortical intracerebral haemorrhages. (**B**) Cortical and cortico-subcortical microhaemorrhages. (**C**) Posterior white matter hyperintensities (WMH). (**D**) Cortical superficial siderosis (cSS). (**E**) White matter perivascular spaces (PVS). (**A**, **B**, **D**) 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].

Lacunes are small fluid-filled cavities located in the deep grey (basal ganglia, thalamus, pons) or white matter (internal or external capsule) (Figure 2**D**), 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 lacunes 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) lacunes have been deemed to be a typical feature of spontaneous DPA [9]. Recent studies, however, suggested there to be an additional association between lobar lacunes and CAA-related haemorrhages [64].

Cortical small DWI hyperintense lesions and microinfarcts (100 μm 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 2**C**), and by deep grey matter hyperintensities in the brainstem [52]. Conversely, CAA-related WMH especially affect the posterior (deep) white matter (Figure 3**C**) 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 2**E**), CAA seems to be related to high numbers of PVS in the hemispheric white matter (especially in the CSO) (Figure 3**E**) [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 arteriolosclerosis 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 Aβ is detectable *in vivo*. Postmortem studies have shown that Aβ-PET tracers mainly label insoluble fibrillar (compact/cored) plaques immunoreactive to either Aβ42 or Aβ40, comprising neuritic Aβ plaques, while amorphous or diffuse Aβ plaques are nearly not detectable [78,79]. Furthermore, quantitative and semiquantitative assessment of Aβ burden using PET correlates well with the postmortem Aβ load in the brain [79,80]. As vascular Aβ 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 Aβ-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 Aβ retention and suggesting the occipital-to-global Aβ-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 Aβ-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 Aβ-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 Aβ-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 anticoagulants 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 APOEε4 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 visuoperceptual 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 Aβ is derived from cellular production (e.g. by neurons and oligodendrocytes) by enzymatic cleavage of the transmembrane amyloid precursor protein. The soluble Aβ protein is eliminated from the brain along the cerebral vascular system by enzymatic degradation, pericytic internalization, transport across the BBB and brain-wide lymphatic Aβ 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 Aβ 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 Aβ elimination from the brain to discuss how those pathways could contribute to the pathophysiological interplay between DPA and CAA.

Physiological Aβ clearance

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

Interstitial Aβ 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 *et al.*, 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 *et al.*, Neurology 2017; Charidimou *et al.*, Neurology 2016 & 2017; Smith *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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		5%
Yakushiji *et al.*, 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 *et al.*,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 *et al.*, 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 *et al.*, 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%
Thijs *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 Aβ 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 Aβ clearance seems further to rely on LRP1–APOE interactions [114]. Plasma Aβ 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 Aβ to prevent free Aβ access to the brain (Figure 4, physiological Aβ elimination) [112,115].

Soluble Aβ 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 Aβ 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 Aβ elimination) [120,121].

Failure of the Aβ 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 Aβ elimination from the brain (Figure 4).

First, age itself has several detrimental effects on different aspects of the Aβ clearance pathways: BBB integrity impairment, endothelial LRP1 expression decrease, BM-associated Aβ 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, Aβ elimination is disturbed by vascular risk factors. Hyperinsulinaemia impairs enzymatic Aβ degradation in a way that insulin and Aβ compete for enzymatic clearance by the insulin-degrading enzyme.

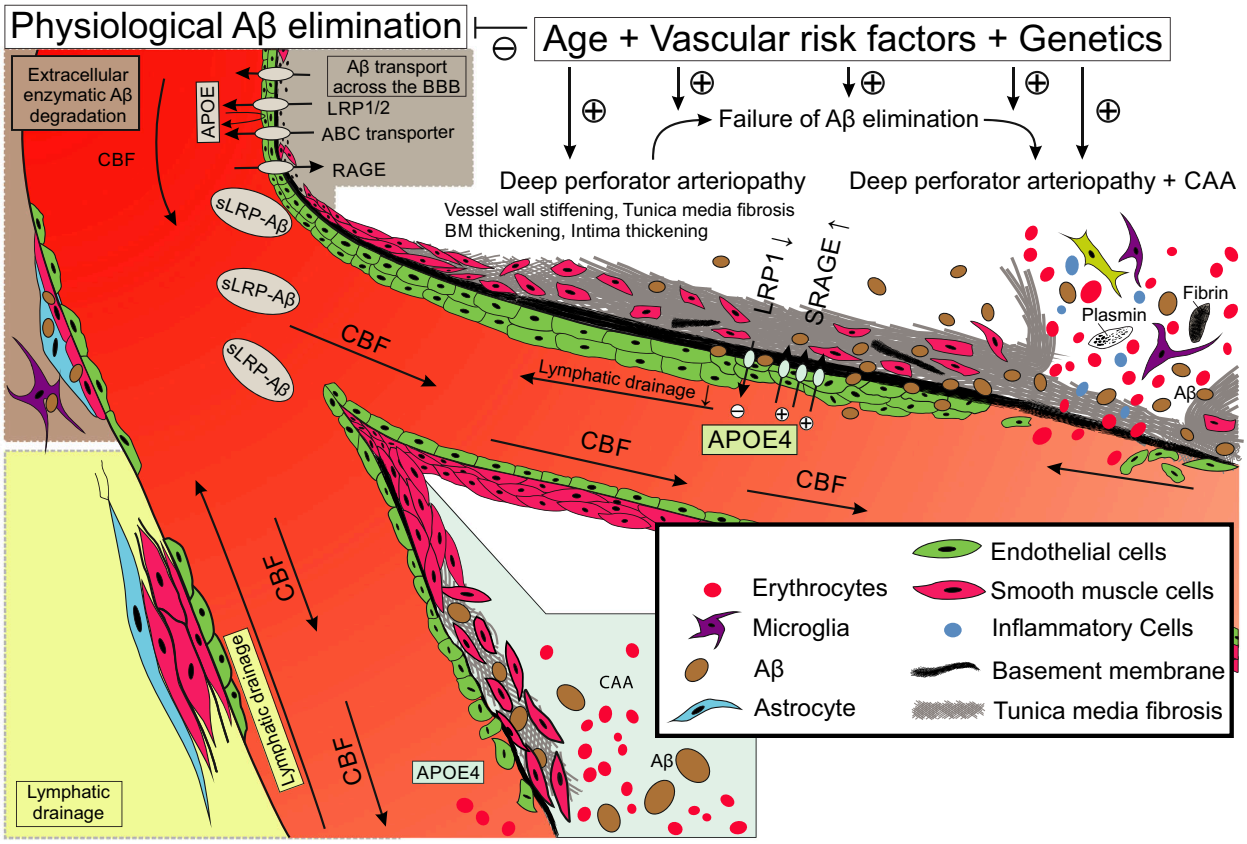

Figure 4. Interaction between deep perforator arteriopathy and cerebral amyloid angiopathy. The left part of the figure demonstrates the physiological elimination of the soluble ß-amyloid (Aß) protein along the cerebral vascular system. This includes: (i) enzymatic degradation through various enzymes 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 Aß 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 Aß 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 Aß drainage mechanisms overall creating a state prone to cerebral amyloid angiopathy (CAA) development. Vascular Aß 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 receptorrelated protein; sLRP-Aß, low-density lipoprotein receptor-related protein Aß 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 Aβ uptake. Moreover, a lifelong high-fat diet and hyperlipidaemia impair lymphatic BM Aβ drainage (Figure 4) [124–126].

Considering genetic aspects, the APOEε4 isoform is less efficient compared to, for example, the APOEε3 or APOEε2 variant at mediating the Aβ elimination. Binding of Aβ to APOEε4 redirects its rapid clearance from LRP1 to the very low-density lipoprotein receptor, which internalizes Aβ/Aβ-APOEε4 complexes more slowly [127]. APOEε4 moreover reduces the Aβ efflux across the BBB through the APOEε4's pro-inflammatory properties (leading to BBB/NVU damage), APOEε4-related LRP1 lowering while increasing RAGE levels or through APOEε4 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 Aβ 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 Aβ clearance from the brain. Besides CSVD itself, its risk factors (age, vascular disease and genetics) additionally have detrimental effects on the Aβ transport mechanisms. Moreover, a vicious circle with small vessel wall damage mediating the effect of risk profile on Aβ 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 Aβ 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 Aβ (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 Aβ 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 Aβ clearance. Further studies that decidedly focus on the Aβ 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 (arteriolosclerosis, 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 Aβ 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 Aβ 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 Aβ retention (taking into account either Aβ PET or CSF Aβ levels) and CSVD features such as WMH. The majority of those studies found a relationship between cerebral Aβ load and CSVD marker burden (e.g. [143,144]), while only few failed (e.g. [145]). There is, moreover, evidence, that greater cortical Aβ 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 Aβ 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 Aβ load. The specific association between vascular Aβ and small vessel wall damage has thus not rigorously been taken into account, while instead thus far rather parenchymal Aβ plaque load has been related to CSVD-associated brain damage.

To better understand the specific interplay between CSVD and the failure of Aβ 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 Aβ40 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 Aβ 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 diethylenetriaminepentacetate) 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 Aβ 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 Aβ 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, arteriolosclerosis 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 Aβ clearance pathways along the damaged small vessel wall
- New biomarkers are needed to detect early small vessel wall damage and related failure of Aβ clearance pathways, to identify patients at risk to develop both DPA and CAA

Abbreviations: Aβ, 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.

References

1 Haffner C, Malik R, Dichgans M. Genetic factors in cerebral small vessel disease and their impact on stroke and dementia. *J Cereb Blood Flow Metab* 2015; **36**: 158–61
2 Banerjee G, Wilson D, Jager HR, Werring DJ. Novel imaging techniques in cerebral small vessel diseases and vascular cognitive impairment. *Biochim Biophys Acta* 2016; **1862**: 926–38. https://doi.org/10.1016/j.bbadis.2015.12.010
3 Charidimou A, Gang Q, Werring DJ. Sporadic cerebral amyloid angiopathy revisited: Recent insights into pathophysiology and clinical spectrum. *J Neurol Neurosurg Psychiatry* 2012; **83**: 124–37
4 Charidimou A, Pantoni L, Love S. The concept of sporadic cerebral small vessel disease: a road map on key definitions and current concepts. *Int J Stroke* 2016; **11**: 6–18
5 Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *Lancet Neurol* 2013; **12**: 483–97

6 Joutel A, Haddad I, Ratelade J, Nelson MT. Perturbations of the cerebrovascular matrisome: a convergent mechanism in small vessel disease of the brain? *J Cereb Blood Flow Metab* 2015; **36**: 143–57

7 Revesz T, Holton JL, Lashley T, Plant G, Frangione B, Rostagno A, *et al*. Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. *Acta Neuropathol* 2009; **118**: 115–30

8 Zhang-Nunes SX, Maat-Schieman ML, van Duinen SG, Roos RA, Frosch MP, Greenberg SM. The cerebral beta-amyloid angiopathies: Hereditary and sporadic. *Brain Pathol* 2006; **16**: 30–9

9 Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010; **9**: 689–701

10 Grinberg LT, Thal DR. Vascular pathology in the aged human brain. *Acta Neuropathol* 2010; **119**: 277–90

11 Ueno M, Sakamoto H, Tomimoto H, Akiguchi I, Onodera M, Huang CL, *et al*. Blood-brain barrier is impaired in the hippocampus of young adult spontaneously hypertensive rats. *Acta Neuropathol* 2004; **107**: 532–8

12 Bailey EL, Wardlaw JM, Graham D, Dominiczak AF, Sudlow CLM, Smith C. Cerebral small vessel endothelial structural changes predate hypertension in stroke-prone spontaneously hypertensive rats: a blinded, controlled immunohistochemical study of 5- to 21-week-old rats. *Neuropathol Appl Neurobiol* 2011; **37**: 711–26

13 Schreiber S, Bueche CZ, Garz C, Kropf S, Angenstein F, Goldschmidt J, *et al*. The pathologic cascade of cerebrovascular lesions in SHRSP: is erythrocyte accumulation an early phase? *J Cereb Blood Flow Metab* 2012; **32**: 278–90

14 Jandke S, Garz C, Schwanke D, Sendtner M, Heinze H-J, Carare RO, *et al*. The association between hypertensive arteriopathy and cerebral amyloid angiopathy in spontaneously hypertensive stroke-prone rats. *Brain Pathol* 2018; **28**: 844–59

15 van der Holst HM, van Uden IWM, Tuladhar AM, de Laat KF, van Norden AGW, Norris DG, *et al*. Factors associated with 8-year mortality in older patients with cerebral small vessel disease: the Radboud University Nijmegen diffusion tensor and magnetic resonance cohort (RUN DMC) study. *JAMA Neurol* 2016; **73**: 402. https://doi.org/10.1001/jamaneurol.2015.4560

16 Wilson D, Charidimou A, Werring DJ. Advances in understanding spontaneous intracerebral hemorrhage: Insights from neuroimaging. *Expert Rev Neurother* 2014; **14**: 661–78

17 Attems J, Jellinger K, Thal DR, van Nostrand W. Review: sporadic cerebral amyloid angiopathy. *Neuropathol Appl Neurobiol* 2011; **37**: 75–93

18 Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, *et al*. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010; **74**: 1346–50

19 Auriel E, Charidimou A, Gurol ME, Ni J, van Etten ES, Martinez-Ramirez S, *et al*. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. *JAMA Neurol* 2016; **73**: 197–202

20 Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, *et al*. Abeta-related angiitis: Primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain* 2005; **128** (Pt 3): 500–15

21 Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. *Ann Neurol* 2004; **55**: 250–6

22 Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al*. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; **12**: 822–38

23 Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol* 2015; **11**: 157–65

24 Reijmer YD, van Veluw SJ, Greenberg SM. Ischemic brain injury in cerebral amyloid angiopathy. *J Cereb Blood Flow Metab* 2015; **36**: 40–54

25 Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. *Lancet Neurol* 2012; **11**: 272–82

26 van Veluw SJ, Shih AY, Smith EE, Chen C, Schneider JA, Wardlaw JM, *et al*. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol* 2017; **16**: 730–40

27 Biffi A, Anderson CD, Battey TW, Ayres AM, Greenberg SM, Viswanathan A, *et al*. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA* 2015; **314**: 904–12

28 Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, *et al*. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. *Neurology* 2008; **70**: 1208–14

29 Benedictus MR, Goos JD, Binnewijzend MA, Muller M, Barkhof F, Scheltens P, *et al*. Specific risk factors for microbleeds and white matter hyperintensities in Alzheimer's disease. *Neurobiol Aging* 2013; **34**: 2488–94

30 Schilling S, DeStefano AL, Sachdev PS, Choi SH, Mather KA, DeCarli CD, *et al*. APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. *Neurology* 2013; **81**: 292–300

31 Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, *et al*. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. *Lancet Neurol* 2011; **10**: 702–9

32 Charidimou A, Jager RH, Peeters A, Vandermeeren Y, Laloux P, Baron JC, *et al*. White matter perivascular

spaces are related to cortical superficial siderosis in cerebral amyloid angiopathy. *Stroke* 2014; **45**: 2930–5
33 Charidimou A, Martinez-Ramirez S, Shoamanesh A, Oliveira-Filho J, Frosch M, Vashkevich A, *et al*. Cerebral amyloid angiopathy with and without hemorrhage: evidence for different disease phenotypes. *Neurology* 2015; **84**: 1206–12
34 Ding J, Sigurdsson S, Garcia M, Phillips CL, Eiriksdottir G, Gudnason V, *et al*. Risk factors associated with incident cerebral microbleeds according to location in older people: the Age, Gene/Environment Susceptibility (AGES)-Reykjavik study. *JAMA Neurol* 2015; **72**: 682–8
35 Romero JR, Preis SR, Beiser A, DeCarli C, Viswanathan A, Martinez-Ramirez S, *et al*. Risk factors, stroke prevention treatments, and prevalence of cerebral microbleeds in the Framingham Heart Study. *Stroke* 2014; **45**: 1492–4
36 Choi JC. Genetics of cerebral small vessel disease. *J Stroke* 2015; **17**: 7–16
37 Charidimou A, Jaunmuktane Z, Baron JC, Burnell M, Varlet P, Peeters A, *et al*. White matter perivascular spaces: an MRI marker in pathology-proven cerebral amyloid angiopathy? *Neurology* 2014; **82**: 57–62
38 Rodrigues MA, Samarasekera N, Lerpiniere C, Humphreys C, McCarron MO, White PM, *et al*. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *Lancet Neurol* 2018; **17**: 232–40
39 Samarasekera N, Rodrigues MA, Toh PS, Al-Shahi S. Imaging features of intracerebral hemorrhage with cerebral amyloid angiopathy: systematic review and meta-analysis. *PLoS ONE* 2017; **12**: e0180923
40 Charidimou A, Imaizumi T, Moulin S, Biffi A, Samarasekera N, Yakushiji Y, *et al*. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: a meta-analysis. *Neurology* 2017; **89**: 820–9
41 Gattringer T, Eppinger S, Beitzke M, Wuensch G, Niederkorn K, Deutschmann H, *et al*. Cortical superficial siderosis and risk of bleeding after thrombolysis for ischemic stroke. *Cerebrovasc Dis* 2015; **40**: 191–7
42 Charidimou A, Shoamanesh A. Clinical relevance of microbleeds in acute stroke thrombolysis: comprehensive meta-analysis. *Neurology* 2016; **87**: 1534–41
43 Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. *Cerebrovasc Dis* 2011; **32**: 528–34
44 Charidimou A, Werring DJ. Cerebral microbleeds and cognition in cerebrovascular disease: an update. *J Neurol Sci* 2012; **322**: 50–5
45 van Veluw SJ, Biessels GJ, Klijn CJM, Rozemuller AJM. Heterogeneous histopathology of cortical microbleeds in cerebral amyloid angiopathy. *Neurology* 2016; **86**: 867–71
46 Wilson D, Werring DJ. Antithrombotic therapy in patients with cerebral microbleeds. *Curr Opin Neurol* 2017; **30**: 38–47
47 Doi H, Inamizu S, Saito BY, Murai H, Araki T, Kira J. Analysis of cerebral lobar microbleeds and a decreased cerebral blood flow in a memory clinic setting. *Intern Med* 2015; **54**: 1027–33
48 Rosand J, Muzikansky A, Kumar A, Wisco JJ, Smith EE, Betensky RA, *et al*. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. *Ann Neurol* 2005; **58**: 459–62
49 Dierksen GA, Skehan ME, Khan MA, Jeng J, Nandigam RN, Becker JA, *et al*. Spatial relation between microbleeds and amyloid deposits in amyloid angiopathy. *Ann Neurol* 2010; **68**: 545–8
50 Kim YJ, Kim HJ, Park JH, Kim S, Woo SY, Kwak KC, *et al*. Synergistic effects of longitudinal amyloid and vascular changes on lobar microbleeds. *Neurology* 2016; **87**: 1575–82
51 van Veluw SJ, Kuijf HJ, Charidimou A, Viswanathan A, Biessels GJ, Rozemuller AJ, *et al*. Reduced vascular amyloid burden at microhemorrhage sites in cerebral amyloid angiopathy. *Acta Neuropathol* 2016; **133**: 409–415
52 Smith EE, Nandigam KR, Chen YW, Jeng J, Salat D, Halpin A, *et al*. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. *Stroke* 2010; **41**: 1933–8
53 Farid K, Charidimou A, Baron J-C. Amyloid positron emission tomography in sporadic cerebral amyloid angiopathy: a systematic critical update. *Neuroimage Clin* 2017; **15**: 247–63
54 Benedictus MR, Prins ND, Goos JD, Scheltens P, Barkhof F, van der Flier WM. Microbleeds, mortality, and stroke in alzheimer disease: the MISTRAL study. *JAMA Neurol* 2015; **72**: 539–45
55 Lauer A, van Veluw SJ, William CM, Charidimou A, Roongpiboonsopit D, Vashkevich A, *et al*. Microbleeds on MRI are associated with microinfarcts on autopsy in cerebral amyloid angiopathy. *Neurology* 2016; **87**: 1488–92
56 Yakushiji Y, Werring DJ. Cerebrovascular disease: lobar cerebral microbleeds signal early cognitive impairment. *Nat Rev Neurol* 2016; **12**: 680–2
57 Charidimou A, Linn J, Vernooij MW, Opherk C, Akoudad S, Baron JC, *et al*. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain* 2015; **138** (Pt 8): 2126–39
58 Greenberg SM, Al Shahi SR, Biessels GJ, van Buchem M, Cordonnier C, Lee JM, *et al*. Outcome markers for clinical trials in cerebral amyloid angiopathy. *Lancet Neurol* 2014; **13**: 419–28
59 Koeppen AH, Michael SC, Li D, Chen Z, Cusack MJ, Gibson WM, *et al*. The pathology of superficial

siderosis of the central nervous system. *Acta Neuropathol* 2008; **116**: 371–82
60 Wollenweber FA, Baykara E, Zedde M, Gesierich B, Achmüller M, Jouvent E, *et al*. Cortical superficial siderosis in different types of cerebral small vessel disease. *Stroke* 2017; **48**: 1404–7
61 Charidimou A, Boulouis G, Gurol ME, Ayata C, Bacskai BJ, Frosch MP, *et al*. Emerging concepts in sporadic cerebral amyloid angiopathy. *Brain* 2017; **140**: 1829–50
62 Charidimou A, Boulouis G, Xiong L, Jessel MJ, Roongpiboonsopit D, Ayres A, *et al*. Cortical superficial siderosis and first-ever cerebral hemorrhage in cerebral amyloid angiopathy. *Neurology* 2017; **88**: 1607–14
63 Gouw AA, Seewann A, van der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, *et al*. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *J Neurol Neurosurg Psychiatry* 2011; **82**: 126–35
64 Pasi M, Boulouis G, Fotiadis P, Auriel E, Charidimou A, Haley K, *et al*. Distribution of lacunes in cerebral amyloid angiopathy and hypertensive small vessel disease. *Neurology* 2017; **88**: 2162–8
65 Duering M, Csanadi E, Gesierich B, Jouvent E, Herve D, Seiler S, *et al*. Incident lacunes preferentially localize to the edge of white matter hyperintensities: Insights into the pathophysiology of cerebral small vessel disease. *Brain* 2013; **136** (Pt 9): 2717–26
66 Fisher CM. Lacunar strokes and infarcts: a review. *Neurology* 1982; **32**: 871–6
67 van Veluw SJ, Biessels GJ, Luijten PR, Zwanenburg JJM. Assessing Cortical Cerebral Microinfarcts on High Resolution MR Images. *J Vis Exp* 2015. https://doi.org/10.3791/53125
68 van Veluw SJ, Hilal S, Kuijf HJ, Ikram MK, Xin X, Yeow TB, *et al*. Cortical microinfarcts on 3T MRI: clinical correlates in memory-clinic patients. *Alzheimers. Dement* 2015; **11**: 1500–9
69 Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019; **18**: 684–696
70 Charidimou A, Boulouis G, Haley K, Auriel E, van Etten ES, Fotiadis P, *et al*. White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology* 2016; **86**: 505–11
71 Charidimou A, Boulouis G, Pasi M, Auriel E, van Etten ES, Haley K, *et al*. MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology* 2017; **88**: 1157–64
72 Dichgans M, Wardlaw J, Smith E, Zietemann V, Seshadri S, Sachdev P, *et al*. METACOHORTS for the study of vascular disease and its contribution to cognitive decline and neurodegeneration: An initiative of the Joint Programme for Neurodegenerative Disease Research. *Alzheimers Dement* 2016; **12**: 1235–49
73 Skrobot OA, Attems J, Esiri M, Hortobagyi T, Ironside JW, Kalaria RN, *et al*. Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment. *Brain* 2016; **139**: 2957–2969
74 Charidimou A, Martinez-Ramirez S, Reijmer YD, Oliveira-Filho J, Lauer A, Roongpiboonsopit D, *et al*. Total magnetic resonance imaging burden of small vessel disease in cerebral amyloid angiopathy: an imaging-pathologic study of concept validation. *JAMA Neurol* 2016; **73**: 994–1001
75 Staals J, Booth T, Morris Z, Bastin ME, Gow AJ, Corley J, *et al*. Total MRI load of cerebral small vessel disease and cognitive ability in older people. *Neurobiol Aging* 2015; **36**: 2806–11
76 Yakushiji Y, Charidimou A, Noguchi T, Nishihara M, Eriguchi M, Nanri Y, *et al*. Total small vessel disease score in neurologically healthy Japanese adults in the Kashima Scan Study. *Intern Med* 2018; **57**: 189–96
77 Charidimou A, Schmitt A, Wilson D, Yakushiji Y, Gregoire SM, Fox Z, *et al*. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): development and assessment of reliability. *J Neurol Sci* 2017; **372**: 178–83
78 Ikonomovic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, *et al*. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain* 2008; **131** (Pt 6): 1630–45
79 Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, *et al*. Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA* 2011; **305**: 275–83
80 Clark CM, Pontecorvo MJ, Beach TG, Bedell BJ, Coleman RE, Doraiswamy PM, *et al*. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. *Lancet Neurol* 2012; **11**: 669–78
81 Gurol ME, Becker JA, Fotiadis P, Riley G, Schwab K, Johnson KA, *et al*. Florbetapir-PET to diagnose cerebral amyloid angiopathy: a prospective study. *Neurology* 2016; **87**: 2043–9
82 Bacskai BJ, Frosch MP, Freeman SH, Raymond SB, Augustinack JC, Johnson KA, *et al*. Molecular imaging with Pittsburgh compound B confirmed at autopsy: a case report. *Arch. Neurol* 2007; **64**: 431–4
83 Charidimou A, Farid K, Tsai H-H, Tsai L-K, Yen R-F, Baron J-C. Amyloid-PET burden and regional distribution in cerebral amyloid angiopathy: a systematic review and meta-analysis of biomarker performance. *J Neurol Neurosurg Psychiatry* 2018; **89**: 410–7
84 Smith EE, Beaudin AE. New insights into cerebral small vessel disease and vascular cognitive impairment from MRI. *Curr Opin Neurol* 2018; **31**: 36–43

85 Maier FC, Wehrl HF, Schmid AM, Mannheim JG, Wiehr S, Lerdkrai C, *et al*. Longitudinal PET-MRI reveals beta-amyloid deposition and rCBF dynamics and connects vascular amyloidosis to quantitative loss of perfusion. *Nat Med* 2014; **20**: 1485–92
86 Crane DE, Black SE, Ganda A, Mikulis DJ, Nestor SM, Donahue MJ, *et al*. Gray matter blood flow and volume are reduced in association with white matter hyperintensity lesion burden: a cross-sectional MRI study. *Front Aging Neurosci* 2015; **7**: 131
87 Gregg NM, Kim AE, Gurol ME, Lopez OL, Aizenstein HJ, Price JC, *et al*. Incidental cerebral microbleeds and cerebral blood flow in elderly individuals. *JAMA Neurol* 2015; **72**: 1021–8
88 Blair GW, Doubal FN, Thrippleton MJ, Marshall I, Wardlaw JM. Magnetic resonance imaging for assessment of cerebrovascular reactivity in cerebral small vessel disease: a systematic review. *J Cereb Blood Flow Metab* 2016; **36**: 833–41
89 Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, *et al*. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. *J Cereb Blood Flow Metab* 2014; **34**: 228–34
90 Salat DH, Smith EE, Tuch DS, Benner T, Pappu V, Schwab KM, *et al*. White matter alterations in cerebral amyloid angiopathy measured by diffusion tensor imaging. *Stroke* 2006; **37**: 1759–64
91 Papma JM, de Groot M, de Koning I, Mattace-Raso FU, van der Lugt A, Vernooij MW, *et al*. Cerebral small vessel disease affects white matter microstructure in mild cognitive impairment. *Hum Brain Mapp* 2014; **35**: 2836–51
92 Reijmer YD, Fotiadis P, Charidimou A, van Veluw SJ, Xiong L, Riley GA, *et al*. Relationship between white matter connectivity loss and cortical thinning in cerebral amyloid angiopathy. *Human Brain Mapp* 2017; **38**: 3723–31.
93 Kim HJ, Im K, Kwon H, Lee JM, Kim C, Kim YJ, *et al*. Clinical effect of white matter network disruption related to amyloid and small vessel disease. *Neurology* 2015; **85**: 63–70
94 Wang R, Fratiglioni L, Laukka EJ, Lovden M, Kalpouzos G, Keller L, *et al*. Effects of vascular risk factors and APOE epsilon4 on white matter integrity and cognitive decline. *Neurology* 2015; **84**: 1128–35
95 Peres R, Guio F, Chabriat H, Jouvent E. Alterations of the cerebral cortex in sporadic small vessel disease: a systematic review of in vivo MRI data. *J Cereb Blood Flow Metab* 2016; **36**: 681–95.
96 Samuraki M, Matsunari I, Yoshita M, Shima K, Noguchi-Shinohara M, Hamaguchi T, *et al*. Cerebral amyloid angiopathy-related microbleeds correlate with glucose metabolism and brain volume in Alzheimer's disease. *J Alzheimers Dis* 2015; **48**: 517–28
97 Appelman APA, Vincken KL, van der Graaf Y, Vlek ALM, Witkamp TD, Mali WPTM, *et al*. White matter lesions and lacunar infarcts are independently and differently associated with brain atrophy: the SMART-MR study. *Cerebrovasc Dis* 2010; **29**: 28–35
98 Fotiadis P, van Rooden S, van der Grond J, Schultz A, Martinez-Ramirez S, Auriel E, *et al*. Cortical atrophy in patients with cerebral amyloid angiopathy: a case-control study. *Lancet Neurol.* 2016; **15**: 811–9
99 Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. *Ann Neurol* 2011; **69**: 320–7
100 Xiong L, Boulouis G, Charidimou A, Roongpiboonsopit D, Jessel MJ, Pasi M, *et al*. Dementia incidence and predictors in cerebral amyloid angiopathy patients without intracerebral hemorrhage. *J Cereb Blood Flow Metab* 2018; **38**: 241–249.
101 Makin SD, Turpin S, Dennis MS, Wardlaw JM. Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. *J Neurol Neurosurg Psychiatry* 2013; **84**: 893–900
102 Reijmer YD, Fotiadis P, Martinez-Ramirez S, Salat DH, Schultz A, Shoamanesh A, *et al*. Structural network alterations and neurological dysfunction in cerebral amyloid angiopathy. *Brain* 2015; **138** (Pt 1): 179–88
103 Valenti R, Charidimou A, Xiong L, Boulouis G, Fotiadis P, Ayres A, *et al*. Visuospatial functioning in cerebral amyloid angiopathy: a Pilot Study. *J Alzheimers Dis* 2017; **56**: 1223–7
104 Chui HC, Ramirez-Gomez L. Clinical and imaging features of mixed Alzheimer and vascular pathologies. *Alzheimers Res Ther* 2015; **7**: 21
105 Kim BJ, Lee SH. Prognostic impact of cerebral small vessel disease on stroke outcome. *J Stroke* 2015; **17**: 101–10
106 Ritter MA, Droste DW, Hegedus K, Szepesi R, Nabavi DG, Csiba L, *et al*. Role of cerebral amyloid angiopathy in intracerebral hemorrhage in hypertensive patients. *Neurology* 2005; **64**: 1233–7
107 Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. *PLoS Medicine* 2009; **6**: e1000180
108 Arvanitakis Z, Capuano AW, Leurgans SE, Buchman AS, Bennett DA, Schneider JA. The relationship of cerebral vessel pathology to brain microinfarcts. *Brain Pathol* 2017; **27**: 77–85
109 Pasi M, Charidimou A, Boulouis G, Auriel E, Ayres A, Schwab KM, *et al*. Mixed-location cerebral hemorrhage/microbleeds: underlying microangiopathy and recurrence risk. *Neurology* 2018; **90**: e119–e126
110 Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy:

validation of the Boston criteria. *Neurology* 2001; **56**: 537–9
111 Neuroscience Nedergaard M. Garbage truck of the brain. *Science* 2013; **340**: 1529–30
112 Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, *et al*. Clearance systems in the brain-implications for Alzheimer disease. *Nat Rev Neurol* 2015; **11**: 457–70
113 Evin G, Weidemann A. Biogenesis and metabolism of Alzheimer's disease Abeta amyloid peptides. *Peptides* 2002; **23**: 1285–97
114 Ma Q, Zhao Z, Sagare AP, Wu Y, Wang M, Owens NC, *et al*. Blood-brain barrier-associated pericytes internalize and clear aggregated amyloid-β42 by LRP1-dependent apolipoprotein E isoform-specific mechanism. *Mol Neurodegener* 2018; **13**: 57
115 Sagare AP, Bell RD, Zlokovic BV. Neurovascular defects and faulty amyloid-beta vascular clearance in Alzheimer's disease. *J Alzheimers Dis* 2013; **33** (Suppl 1): S87–100
116 Weller RO, Nicoll JA. Cerebral amyloid angiopathy: Pathogenesis and effects on the ageing and Alzheimer brain. *Neurol Res* 2003; **25**: 611–6
117 Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, *et al*. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med* 2012; **4**: 147ra111
118 Thrane AS, Rangroo T, Plog BA, Nedergaard M. Filtering the muddied waters of brain edema. *Trends Neurosci* 2015; **38**: 333–5
119 Weller RO, Djuanda E, Yow HY, Carare RO. Lymphatic drainage of the brain and the pathophysiology of neurological disease. *Acta Neuropathol* 2009; **117**: 1–14
120 Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JA, Perry VH, *et al*. Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: significance for cerebral amyloid angiopathy and neuroimmunology. *Neuropathol Appl Neurobiol* 2008; **34**: 131–44
121 Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman A, Plog BA, Liao Y, *et al*. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *J Neurosci* 2013; **33**: 18190–9
122 Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: a Beginner's guide. *Neurochem Res* 2015; **40**: 2583–99
123 Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, *et al*. Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol* 2014; **76**: 845–61
124 Carnevale D, Mascio G, D'Andrea I, Fardella V, Bell RD, Branchi I, *et al*. Hypertension induces brain beta-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension* 2012; **60**: 188–97
125 Hawkes CA, Gentleman SM, Nicoll JA, Carare RO. Prenatal high-fat diet alters the cerebrovasculature and clearance of beta-amyloid in adult offspring. *J Pathol* 2015; **235**: 619–31
126 Jiang Q, Zhang L, Ding G, Davoodi-Bojd E, Li Q, Li L, *et al*. Impairment of the glymphatic system after diabetes. *J Cereb Blood Flow Metab* 2017; **37**: 1326–1337
127 Deane R, Sagare A, Hamm K, Parisi M, Lane S, Finn MB, *et al*. apoE isoform-specific disruption of amyloid beta peptide clearance from mouse brain. *J Clin Invest* 2008; **118**: 4002–13
128 Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, *et al*. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. *Nature* 2012; **485**: 512–6
129 Halliday MR, Rege SV, Ma Q, Zhao Z, Miller CA, Winkler EA, *et al*. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *J Cereb Blood Flow Metab* 2016; **36**: 216–27
130 Hawkes CA, Sullivan PM, Hands S, Weller RO, Nicoll JA, Carare RO. Disruption of arterial perivascular drainage of amyloid-beta from the brains of mice expressing the human APOE epsilon4 allele. *PLoS ONE* 2012; **7**: e41636
131 Tai LM, Thomas R, Marottoli FM, Koster KP, Kanekiyo T, Morris AW, *et al*. The role of APOE in cerebrovascular dysfunction. *Acta Neuropathol* 2016; **131**: 709–23
132 Zlokovic BV. Cerebrovascular effects of apolipoprotein E: Implications for Alzheimer disease. *JAMA Neurol* 2013; **70**: 440–4
133 Gaberel T, Gakuba C, Goulay R, Martinez DL, Hanouz JL, Emery E, *et al*. Impaired glymphatic perfusion after strokes revealed by contrast-enhanced MRI: a new target for fibrinolysis? *Stroke* 2014; **45**: 3092–6
134 Iliff JJ, Nedergaard M. Is there a cerebral lymphatic system? *Stroke* 2013; **44** (6 Suppl 1): S93–S95
135 Weller RO, Yow HY, Preston SD, Mazanti I, Nicoll JA. Cerebrovascular disease is a major factor in the failure of elimination of Abeta from the aging human brain: Implications for therapy of Alzheimer's disease. *Ann N Y Acad Sci* 2002; **977**: 162–8
136 Weller RO, Nicoll JA. Cerebral amyloid angiopathy: both viper and maggot in the brain. *Ann Neurol* 2005; **58**: 348–50
137 Wuerfel J, Haertle M, Waiczies H, Tysiak E, Bechmann I, Wernecke KD, *et al*. Perivascular spaces–MRI marker of inflammatory activity in the brain? *Brain* 2008; **131** (Pt 9): 2332–40
138 Grinberg LT, Korczyn AD, Heinsen H. Cerebral amyloid angiopathy impact on endothelium. *Exp Gerontol* 2012; **47**: 838–42

139 Gentile MT, Poulet R, Di Pardo A, Cifelli G, Maffei A, Vecchione C, *et al*. Beta-amyloid deposition in brain is enhanced in mouse models of arterial hypertension. *Neurobiol Aging* 2009; **30**: 222–8
140 Giannoni P, Arango-Lievano M, Neves ID, Rousset M-C, Baranger K, Rivera S, *et al*. Cerebrovascular pathology during the progression of experimental Alzheimer's disease. *Neurobiol Dis* 2016; **88**: 107–17
141 Pirici D, Stanaszek L, Garz C, Niklass S, Heinze HJ, Kalinski T, *et al*. Common impact of chronic kidney disease and brain microhemorrhages on cerebral Abeta pathology in SHRSP. *Brain Pathol* 2017; **27**: 169–80
142 Held F, Morris AWJ, Pirici D, Niklass S, Sharp MMG, Garz C, *et al*. Vascular basement membrane alterations and β-amyloid accumulations in an animal model of cerebral small vessel disease. *Clin Sci* 2017; **131**: 1001–13
143 van Westen D, Lindqvist D, Blennow K, Minthon L, Nagga K, Stomrud E, *et al*. Cerebral white matter lesions - associations with Abeta isoforms and amyloid PET. *Sci Rep* 2016; **6**: 20709
144 Shams S, Granberg T, Martola J, Charidimou A, Li X, Shams M, *et al*. Cerebral microbleeds topography and cerebrospinal fluid biomarkers in cognitive impairment. *J Cereb Blood Flow Metab* 2017; **37**: 1006–1013
145 Charidimou A, Hong YT, Jager HR, Fox Z, Aigbirhio FI, Fryer TD, *et al*. White matter perivascular spaces on magnetic resonance imaging: marker of cerebrovascular amyloid burden? *Stroke* 2015; **46**: 1707–9
146 Provenzano FA, Muraskin J, Tosto G, Narkhede A, Wasserman BT, Griffith EY, *et al*. White matter hyperintensities and cerebral amyloidosis: necessary and sufficient for clinical expression of Alzheimer disease? *JAMA Neurol* 2013; **70**: 455–61
147 Charidimou A, Friedrich JO, Greenberg SM, Viswanathan A. Core CSF biomarker profile in cerebral amyloid angiopathy: a meta-analysis. *Neurology* 2018; **90**: e754–62. https://doi.org/10.1212/WNL.0000000000005030
148 Steinacker P, Feneberg E, Weishaupt J, Brettschneider J, Tumani H, Andersen PM, *et al*. Neurofilaments in the diagnosis of motoneuron diseases: a prospective study on 455 patients. *J Neurol Neurosurg Psychiatry* 2016; **87**: 12–20
149 Gattringer T, Pinter D, Enzinger C, Seifert-Held T, Kneihsl M, Fandler S, *et al*. Serum neurofilament light is sensitive to active cerebral small vessel disease. *Neurology* 2017; **89**: 2108–14
150 Zhang CE, Wong SM, van de Haar HJ, Staals J, Jansen JFA, Jeukens CRLPN, *et al*. Blood-brain barrier leakage is more widespread in patients with cerebral small vessel disease. *Neurology* 2017; **88**: 426–32
151 Montagne A, Nation DA, Pa J, Sweeney MD, Toga AW, Zlokovic BV. Brain imaging of neurovascular dysfunction in Alzheimer's disease. *Acta Neuropathol* 2016; **131**: 687–707
152 Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, *et al*. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J Clin Invest* 2013; **123**: 1299–309
153 Cocker LJ, Lindenholz A, Zwanenburg JJ, van der Kolk AG, Zwartbol M, Luijten PR, *et al*. Clinical vascular imaging in the brain at 7T. *NeuroImage* 2018; **168**: 452–8
154 Bouvy WH, Geurts LJ, Kuijf HJ, Luijten PR, Kappelle LJ, Biessels GJ, *et al*. Assessment of blood flow velocity and pulsatility in cerebral perforating arteries with 7-T quantitative flow MRI. *NMR Biomed* 2016; **29**: 1295–304
155 Betts MJ, Acosta-Cabronero J, Cardenas-Blanco A, Nestor PJ, Düzel E. High-resolution characterisation of the aging brain using simultaneous quantitative susceptibility mapping (QSM) and R2* measurements at 7T. *NeuroImage* 2016; **138**: 43–63

Received 8 February 2019
Accepted after revision 11 July 2019
Published online Article Accepted on 6 August 2019