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MRI-visible perivascular space locations distinguishes Alzheimer's disease from subcortical vascular cognitive impairment independently of amyloid burden

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Running title:

Perivascular spaces and dementia diagnosis

Abstract

MRI-visible perivascular spaces are a neuroimaging marker of cerebral small vessel disease. Their location may relate to the type of underlying small vessel pathology: those in the white matter centrum semi-ovale have been associated with cerebral amyloid angiopathy, whilst those in the basal ganglia have been associated with deep perforating artery arteriolosclerosis. Since cerebral amyloid angiopathy is an almost invariable pathological finding in Alzheimer's disease, we hypothesized that MRI-visible perivascular spaces in the centrum semi-ovale would be associated with a clinical diagnosis of Alzheimer's disease, whereas those in the basal ganglia would be associated with subcortical vascular cognitive impairment. We also hypothesised that MRI-visible perivascular spaces in the centrum semi-ovale would be associated with brain amyloid burden, as detected by amyloid-PET using [^{11}C] Pittsburgh B compound (PiB-PET). 226 patients (Alzheimer's disease n=110; subcortical vascular cognitive impairment n=116) with standardised MRI and PiB-PET imaging were included. MRI-visible perivascular spaces were rated using a validated 4-point visual rating scale, and then categorised by severity ("none/mild", "moderate" or "frequent/severe"). Univariable and multivariable regression analyses were performed. Those with Alzheimer's disease related cognitive impairment were younger, more likely to have a positive amyloid-PET scan and carry at least one Apolipoprotein E ε4 allele; those with subcortical vascular cognitive impairment were more likely to have hypertension, diabetes mellitus, hyperlipidaemia, prior stroke, lacunes, deep microbleeds, and carry the Apolipoprotein E ε3 allele. In adjusted analyses, the severity of MRI-visible perivascular spaces in the centrum semi-ovale was independently associated with clinically diagnosed Alzheimer's disease (frequent/severe grade Odds Ratio, OR, ~~7.69~~6.26, 95% CI~~–~~1.66 to 23.58~~4.29 to 20.71~~; p=~~0.0003~~0.017, compared with none/mild grade), whereas the severity of MRI-visible perivascular spaces in the basal ganglia was associated with clinically diagnosed

subcortical vascular cognitive impairment and negatively predicted Alzheimer's disease (frequent/severe grade OR 0.035, 95% CI 0.01–00 to 0.4744; p=0.00904, compared with none/mild grade). MRI-visible perivascular space severity in either location did not predict amyloid-PET positivity. These findings provide further evidence that the anatomical distribution of MRI-visible perivascular spaces may reflect the underlying cerebral small vessel disease. Using MRI-visible perivascular space location and severity together with other imaging markers may improve the diagnostic value of neuroimaging in memory clinic populations, in particular in differentiating between clinically diagnosed Alzheimer's and subcortical vascular cognitive impairment.

Keywords:

Perivascular space, Alzheimer's disease, subcortical vascular cognitive impairment, cerebral amyoid angiopathy, amyloid PET

Abbreviations:

Aβ	Amyloid beta
AD	Alzheimer's disease
ADCI	Alzheimer's disease related cognitive impairment (aMCI & AD)
aMCI	Amnestic mild cognitive impairment
APOE	Apolipoprotein E
BG	Basal ganglia
CAA	Cerebral amyloid angiopathy
CI	Confidence Interval
CMB	Cerebral microbleed
CSO	Centrum semi-ovale
cSS	Cortical superficial siderosis
ICH	Intracerebral haemorrhage
IQR	Interquartile range
OR	Odds ratio
PiB	11-Carbon based Pittsburgh compound B
PVS	Perivascular space (MRI-visible)
SD	Standard deviation
SVaD	Subcortical vascular dementia
svMCI	Subcortical vascular MCI

SVCI Subcortical vascular cognitive impairment (svMCI & SVaD)

Introduction

Small vessel diseases of the brain are an important cause of stroke and dementia (Pantoni, 2010; Bath and Wardlaw, 2015). Our ability to accurately identify these diseases using neuroimaging markers has improved considerably in recent years (Wardlaw *et al.*, 2013c), with increasing interest in the role of small vessel pathology in traditionally "non-vascular" dementias, such as Alzheimer's disease (AD). The most common age-related cerebral small vessel disease subtypes are: arteriolosclerosis and related processes affecting deep perforating arteries (often termed hypertensive arteriopathy); and cerebral amyloid angiopathy (CAA) (Pantoni, 2010). Arteriolosclerosis is associated with hypertension, diabetes and increasing age, and "vascular" dementia (the most common form of which is subcortical vascular cognitive impairment, SVCI), whereas CAA is the result of amyloid-beta (Aβ) deposition in the walls of small to medium vessels in the cortex and leptomeninges, and found in over 90% of those with AD (Charidimou *et al.*, 2012). As well as being a risk factor for spontaneous intracerebral haemorrhage (Samarasekera *et al.*, 2012), CAA can result in cognitive deficits independently of AD (Arvanitakis *et al.*, 2011; Boyle *et al.*, 2015; Reijmer *et al.*, 2015), although the exact interaction between these two processes remains unclear. Traditionally AD and SVCI have been described as having distinct neuroimaging profiles (Wardlaw *et al.*, 2013b; Greenberg *et al.*, 2014), but clinically differentiating between the two remains difficult, as both the cognitive symptoms and the imaging findings frequently overlap (Lee *et al.*, 2011; Wardlaw *et al.*, 2013a; Wardlaw *et al.*, 2013b; Greenberg *et al.*, 2014; Lee *et al.*, 2014). Given this, identifying new markers that further improve our ability to discriminate between AD and SVCI remains both relevant and important, in particular with regard to recruitment for clinical trials investigating pharmacological interventions (Ahmed *et al.*, 2014; Andrieu *et al.*, 2015).

MRI-visible perivascular spaces (PVS) - sometimes termed Virchow-Robin spaces, type 3 lacunes and *état crible* - are hypothesised to result from an enlargement of the potential space within the wall of a cerebral blood vessel, possibly secondary to impaired interstitial fluid drainage (Wardlaw *et al.*, 2013b; Weller *et al.*, 2015). Whereas enlargement in the basal ganglia (BG-PVS) appears to be associated with markers of arteriolosclerosis, enlargement of PVS in the white matter centrum semi-ovale (CSO-PVS) appears to be associated with cerebral Aβ pathologies, both AD and CAA (Charidimou *et al.*, 2013a; Charidimou *et al.*, 2013b; Martinez-Ramirez *et al.*, 2013). Neuropathological studies have demonstrated that the frequency and severity of white matter PVS is greater in AD than controls, and this was associated with brain Aβ load, severity of CAA and Apolipoprotein E (*APOE*) ε4 presence (Roher *et al.*, 2003). The association of AD and increased white matter PVS volume has also been demonstrated using neuroimaging (Ramirez *et al.*, 2015). PVS in the centrum semi-ovale (CSO-PVS) are associated with CAA-related intracerebral haemorrhage (ICH) (Charidimou *et al.*, 2013b; Charidimou *et al.*, 2014b) and its "haemorrhagic" markers, namely lobar microbleeds (Martinez-Ramirez *et al.*, 2013; Yakushiji *et al.*, 2014) and cortical superficial siderosis (Charidimou *et al.*, 2014a). Indeed, a recent study using post-mortem 7-Tesla MR in CAA-related ICH found an association between juxta-cortical PVS enlargement and the histopathological grade of CAA in the overlying cortex (van Veluw *et al.*, 2015). In addition, a small study of patients with CAA-related ICH and healthy controls found an association between amyloid-PET burden (as measured using 11-Carbon based Pittsburgh compound B, PiB) and CSO-PVS (Charidimou *et al.*, 2015). This makes PVS topography in certain clinical contexts a promising new marker of cerebral small vessel diseases. However, the relationships between PVS topography, amyloid deposition and clinical dementia syndromes (AD and SVCI) are not well understood.

We aimed to further evaluate this association of PVS location with small vessel disease type in a cohort of patients with AD related cognitive impairment (ADCI; either AD or AD mild cognitive impairment) and SVCI (either subcortical vascular dementia or subcortical vascular mild cognitive impairment). We hypothesised that ADCI is associated with CSO-PVS (as these patients are likely to have CAA), but not BG-PVS, which instead is associated with SVCI (and arteriolosclerosis). We also hypothesised that, given the CSO-PVS are associated with cerebral Aβ diseases, CSO-PVS is associated with PiB positivity, whereas BG-PVS would not demonstrate any such association.

Materials & Methods

Participants

We prospectively recruited 251 subjects with cognitive impairment who underwent PiB-PET and structural brain MRI, between July 2007 and July 2011. We included 45 patients with amnestic mild cognitive impairment (aMCI), 69 with probable AD dementia, 67 with subcortical vascular MCI (svMCI), and 70 with subcortical vascular dementia (SVaD); all patients had been clinically diagnosed at Samsung Medical Center. Of these, 226 subjects were included in the current study, with exclusions made either due to imaging being unavailable (n = 20) or too degraded by motion artefact to be interpreted (n = 5). Probable AD dementia patients fulfilled diagnostic criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (McKhann *et al.*, 1984). Patients with SVaD met the diagnostic criteria for

vascular dementia as determined by the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), and also fulfilled the imaging criteria for SVaD proposed by Erkinjuntti et al (Erkinjuntti *et al.*, 2000). Patients with aMCI and svMCI met Petersen's criteria for MCI with modifications (Seo *et al.*, 2009). All svMCI and SVaD patients had severe white matter hyperintensities (WMH) on their MRI scans, which was defined as a cap or band (periventricular WMH) ≥10mm and deep WM lesions (deep WMH) ≥25mm, as modified from the Fazekas ischemia criteria (Fazekas *et al.*, 1993). All aMCI and AD patients were classified as having minimal (periventricular WMH <5mm and deep WMH <5mm) or moderate WMH (between minimal and severe grades). These WMH definitions are in line with those recently proposed to describe WMH of presumed vascular origin (Wardlaw *et al.*, 2013c). Patients with aMCI or AD were considered to have AD-related cognitive impairment (ADCI), whereas those with svMCI or SVaD were considered to have subcortical vascular cognitive impairment (SVCI). We excluded patients with territorial infarctions and those with WMH due to radiation injury, multiple sclerosis, vasculitis, or leukodystrophy. All patients completed a clinical interview and neurological examination. Blood tests included a complete blood count, blood chemistry test, vitamin B_{12}/folate measurement, syphilis serology, thyroid function test, and *APOE* genotyping.

We obtained written consent from each patient, and the study protocol was approved by the Institutional Review Board of the Samsung Medical Center.

PiB-PET acquisition and data analysis

[^{11}C] PiB-PET scanning was performed on all participants at Samsung or Asan Medical Center using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI) in 3-dimensional scanning mode that examined 35 slices of 4.25-mm thickness spanning the entire

brain. [^{11}C] PiB was injected into an antecubital vein as a bolus with a mean dose of 420 MBq (i.e., range 259–550 MBq). A CT scan was performed for attenuation correction 60 minutes after injection. A 30-minute emission static PET scan was then initiated. The specific radioactivity of [^{11}C] PiB at the time of administration was more than 1,500 Ci/mmol for patients and the radiochemical yield was more than 35%. The radiochemical purity of the tracer was more than 95% in all PET studies.

PiB PET images were co-registered to individual MRIs, which were normalized to a T1-weighted MRI template. Using these parameters, MRI co-registered PiB PET images were normalized to the MRI template. The quantitative regional values of PiB retention on the spatially normalized PiB images were obtained by an automated VOIs analysis using the automated anatomical labeling (AAL) atlas. Data processing was performed using SPM Version 5 (SPM5) within Matlab 6.5 (MathWorks, Natick, MA).

To measure PiB retention, we used the cerebral cortical region to cerebellum uptake ratio. The cerebellum was used as a reference region as it did not show group differences. We selected 28 cortical VOIs from left and right hemispheres using the AAL atlas. The cerebral cortical VOIs that were chosen for this study consisted of the bilateral frontal (superior and middle frontal gyri, the medial portion of superior frontal gyrus, the opercular portion of inferior frontal gyrus, the triangular portion of inferior frontal gyrus, supplementary motor area, orbital portion of the superior, middle, and inferior orbital frontal gyri, rectus and olfactory cortex), posterior cingulate gyri, parietal (superior and inferior parietal, supramarginal and angular gyri, and precuneus), lateral temporal (superior, middle and inferior temporal gyri, and heschl gyri), and occipital (superior, middle, and inferior occipital gyri, cuneus, calcarine fissure, and lingual and fusiform gyri). Regional cerebral cortical

uptake ratios were calculated by dividing each cortical VOI's uptake ratio by the mean uptake of the cerebellar cortex (cerebellum crus1 and crus2). Global PiB uptake ratio was calculated from the volume-weighted average uptake ratio of bilateral 28 cerebral cortical VOIs. Patients were considered PiB-positive if their global PiB retention ratio was over 1.5 from the mean of the normal control (Lee *et al.*, 2011).

MR imaging techniques

Standardized T1, T2, T2* gradient echo (GRE), and 3D fluid-attenuated inversion recovery (FLAIR) images were acquired from all subjects at Samsung Medical Center using the same 3.0T MRI scanner (Philips 3.0T Achieva). In all subjects, these images were obtained in one session and all MR images were obtained in the same orientation and slice positions. T2* GRE-MRI were obtained using the following parameters: axial slice thickness, 5.0mm; inter-slice thickness, 2mm; TR, 669ms; TE 16ms; flip angle, 18°, and matrix size of 560x 560 pixels. We acquired the 3D FLAIR images with the following imaging parameters: axial slice thickness of 2 mm; no gap; TR of 11000 msec; TE of 125 msec; flip angle of 90°; and matrix size of 512 × 512 pixels.

Measurement of WMH volume

WMH volume (in millilitres) was quantified on FLAIR images using an automated method (Jeon *et al.*, 2011). Because the contrasting properties of FLAIR images allow automated segmentation and classification of WMH (Sachdev *et al.*, 2004), we used FLAIR images to quantify WMH. The procedures for measuring regional WMH volume have been previously described (Jeon *et al.*, 2011). First, we extracted the WMH candidate regions using T1-weighted images to avoid misclassification in the subarachnoid space and CSF interface, which cannot be excluded by intensity threshold or the conventional brain extraction tools.

Second, in order to extract WMH, a threshold method was applied to the FLAIR images after using the WMH candidate mask. Even though the threshold value was selected after intensity normalization, segmented results could contain the false positive or negative depending on the extent of WMH. Therefore, if the results were found to contain an error, the threshold value was reselected through visual inspection by two raters.

Lacune assessment on MRI

A lacune was defined as a lesion ≥3mm and ≤15mm in diameter with low signal on T1 imaging, high signal on T2-weighted imaging, and with a perilesional halo on FLAIR imaging. Two experienced neurologists who were blinded to the patients' clinical data reviewed the number and location of the lacunes on 80 axial FLAIR slices. This meets the recently proposed definition of a lacune of presumed vascular origin (Wardlaw *et al.*, 2013c). Two neurologists manually counted the number of lacunes, with a kappa value of 0.78.

Analysis of CMBs on gradient echo MRI

CMBs were defined as lesions ≤10mm in diameter and were also defined using criteria proposed by Greenberg *et al.*(Greenberg *et al.*, 2009). Two experienced neurologists, who were blinded to patient data, reviewed the number and location of CMBs on 20 T2 GRE-MRI axial slices. The two neurologists had an agreement kappa value for the presence of CMBs of 0.92, and a consensus was reached in any case of discrepancy.

CMBs were counted in four lobar regions (frontal, temporal, parietal, occipital) and also in deep brain regions. A lobar region was defined as tissue ≤10 mm from the brain surface.

Quantification of PVS

PVS were defined and rated on axial T2-weighted MR images, according to STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) (Wardlaw *et al.*, 2013c), by a trained observer who was blinded to the clinical information (GB) using a validated 4-point visual rating scale (0 = no PVS, 1 = <10 PVS, 2 = 11-20 PVS, 3 = 21-40 PVS and 4 = >40 PVS) in the basal ganglia and centrum semi-ovale (cerebral hemisphere white matter) (Maclullich *et al.*, 2004; Doubal *et al.*, 2010). Rating was carried out on a single pre-defined slice (first slice above the anterior commissure in the basal ganglia; the first slice above the level of the lateral ventricles for the centrum semi-ovale). Both hemispheres were counted, and the hemisphere with the highest score was recorded. Severity was defined as "none/mild" (equivalent to rating scale categories 0 and 1), "moderate" (rating scale category 2), and "frequent/severe" (rating scale categories 3 and 4) in order to generate groups of a similar size for meaningful subsequent statistical analysis. Figure 1 demonstrates PVS examples of each severity grade in both locations.

Statistical Analysis

Baseline characteristics were compared using Chi-squared or Fishers exact tests for categorical variables, independent t-tests for normally distributed continuous variables and Mann-Whitney U tests for continuous variables that were not normally distributed. PVS (both CSO-PVS and BG-PVS) were considered as categorical variables, subdivided by severity as described above. Univariable and multivariable logistic regression analyses were performed; variables of interest in univariable analysis were included in the multivariable models. WMH volume and lacune burden were not included in the analysis for predictors of diagnosis, as these variables had been used to make the original clinical diagnosis.

Statistical analysis was performed with Stata (Version 11.2).

Results

PVS topography as a predictor of clinical diagnosis

The comparison of baseline characteristics of the ADCI and SVCI groups are shown in Table 1. Those in the ADCI group were younger (a mean 70.3 years vs 73.8 years, p = 0.0012), more likely to be PiB positive (78.2% vs 29.3%, p <0.0001) and carry the *APOE* ε4 allele (48.6% vs 25.7%, p <0.0001). Those in the SVCI group were more likely to have hypertension (77.6% vs 47.3%, p <0.0001), diabetes mellitus (25.9% vs 13.6%, p = 0.021), hyperlipidemia (36.2% vs 23.6%, p = 0.039), and prior stroke (26.7% vs 5.4%, p <0.0001). They were also more likely to carry the *APOE* ε3 allele (97.4% vs 86.9%, p = 0.004) and have lacunes (median 9 vs 0, p <0.0001) and deep CMBs (53.5% vs 6.5%, p <0.0001).

In univariable logistic regression analysis, increasing CSO-PVS severity was a positive predictor of ADCI; individuals with moderate CSO-PVS had an OR of 4.16 (95% CI: 2.08 to 8.29) and those with frequent/severe CSO-PVS had an OR of 9.43 (95% CI: 4.29 to 20.71) compared to those with none/mild CSO-PVS (Table 2). Increasing severity of BG-PVS was negatively associated with ADCI (i.e. positively associated with a clinical diagnosis of SVCI); individuals with moderate BG-PVS had an OR for ADCI of 0.10 (95% CI: 0.04 to 0.26) and those with frequent/severe BG-PVS had an OR of 0.06 (95% CI: 0.01 to 0.47) compared to those with none/mild BG-PVS. After adjustment for other confounding variables, all of these associations remained: increasing CSO-PVS severity was a positive predictor of clinically diagnosed ADCI (none/mild as reference group: moderate severity, OR ~~5.40~~3.57, 95% CI 1.17 to 10.89~~2.08 to 8.29~~; frequent/severe, OR 6.26~~7.69~~, 95% CI 1.66 to 23.58~~4.29 to 20.71~~). Increasing severity of BG-PVS was negatively associated with ADCI and thus predictive of clinically diagnosed SVCI (none/mild as reference group: moderate

severity, OR 0.2614, 95% CI 0.074 to 1.01)0.26; frequent/severe, OR 0.035, 95% CI 0.001 to 0.447). Younger age, PiB positivity, the absence of hyperlipidaemia and number of lacunes the absence of deep CMBs were also associated with a diagnosis of ADCI after adjustment.

PVS topography as a predictor of PiB positivity

The baseline characteristics of the PiB positive and negative groups are given in Table 3. Those in the PiB positive group were more likely to have a diagnosis of ADCI (71.7% vs 22.6%, p <0.0001), carry the *APOE* ε4 allele (53.9% vs 17.5%, p <0.0001) and have cSS, although the numbers were small (5.8% vs 0.9%, p = 0.047). They were less likely to have hypertension (50.0% vs 77.4%, p <0.0001), diabetes mellitus (15.0% vs 25.5%, p = 0.049), previous stroke (8.3% vs 25.5%, p = 0.001) and the *APOE* ε3 allele (86.3% vs 99.0%, P <0.0001). They were had a lower WMH volume (median 5.2ml vs 29.9ml, p <0.00001), fewer lacunes (median 0 vs 7, p <0.00001) and a lower presence of deep microbleeds (16.8% vs 46.7%, p <0.0001).

In univariable logistic regression analysis increasing CSO-PVS severity was a positive predictor of PiB positivity; individuals with moderate CSO-PVS had an OR of 1.37 (95% CI: 0.74 to 2.54) and those with frequent/severe CSO-PVS had an OR of 2.50 (95% CI: 1.24 to 5.04) compared to those with none/mild CSO-PVS, respectively (Table 4). However, after adjustment for other factors, there was no relationship between CSO-PVS severity and PiB positivity. BG-PVS severity was not associated with PiB positivity. The only variables that remained independently associated with PiB positivity were ADCI diagnosis, presence of the *APOE* ε4 allele and number of lacunes.

Discussion

CSO-PVS severity is strongly associated with clinically diagnosed ADCI whereas BG-PVS severity predicts clinically diagnosed SVCI. However, CSO-PVS severity was not independently associated with PiB positivity. There are two possible interpretations of this lack of independent association between CSO-PVS with PiB amyloid retention: either CSO-PVS are associated with ADCI as a marker of amyloid pathology that cannot be accurately resolved by amyloid-PET, or CSO-PVS are indicative of an amyloid-independent pathology.

Our findings are consistent with previous findings of an association between CSO-PVS and both AD and CAA, both of which are associated with Aβ deposition (Charidimou *et al.*, 2012). One reason for the apparent lack of independent association between CSO-PVS and PiB might be that PiB-PET is unable to resolve smaller blood vessels affected by CAA. This is supported by neuropathological evidence that, although severity of CAA does appear associated with CSO-PVS in AD, the CAA affected vessels are predominantly less than 500μm in diameter, which may be too small to be identified using PiB-PET (Roher *et al.*, 2003). Alternatively, the PiB-PET signal observed in our ADCI cohort may be more a measure of parenchymal Aβ (this being the predominant signal) and be unrepresentative of the true vascular Aβ; PiB-PET binding has been shown to be lower in patients with CAA compared to those with AD (Johnson *et al.*, 2007). Thus it is possible that any sequelae of vascular amyloid deposition, for example impaired interstitial fluid drainage secondary to a failure to adequately clear pathological proteins, could still be visible as MRI-visible CSO-PVS (Weller *et al.*, 2015), independently of PiB positivity.

An alternative explanation is that CSO-PVS are associated with ADCI but not PiB positivity because they are manifestations of an amyloid-independent process, for example a tau protein

related process. As well as being a core neuropathological finding in AD, neurofibrillary tangles have been demonstrated in association with CAA in patients with AD (Jeynes and Provias, 2006), and tau deposits (neurofibrillary tangles and pretangles) have been described in Aβ-related angiitis, an inflammatory form of CAA (Kurian *et al.*, 2012). One study reviewing perivascular hyperphosphorylated tau in patients with AD found higher levels surrounding the CAA affected vessels than the unaffected ones (Williams *et al.*, 2005). Thus it is possible that CAA could impair perivascular drainage, leading to tau aggregation, which could further impair perivascular drainage leading to further tau aggregation and so on (a "feed-forward" loop), with MRI-visible perivascular spaces being the end result (Weller *et al.*, 2009; Love and Miners, 2015). In animal models, traumatic brain injury appears to disrupt normal perivascular clearance for at least 28 days, resulting in the accumulation of hyper-phosphorylated tau (Iliff *et al.*, 2014); CAA could impair perivascular drainage in a similar way. Alternatively CAA may disrupt perivascular drainage via perturbations in normal arteriolar pulsation (Hawkes *et al.*, 2014; Kress *et al.*, 2014). It is also possible that the presence of hyper-phosphorylated tau has direct deleterious consequences for perivascular astrocytes, for example by directly disrupting their microtubular structure, or altering the expression or localisation of membrane channels (for example, aquaporin 4) that change normal interstitial fluid dynamics, with the eventual outcome of an enlarged perivascular space (Arima *et al.*, 1998; Thrane *et al.*, 2014; Iqbal *et al.*, 2016).

This study has some limitations. Firstly, this is an observational study without healthy aged matched controls for comparison; despite this, our findings are generally in keeping with previous reports from AD and SVCI cohorts. A previous study (Charidimou *et al.*, 2015) has demonstrated an association between PiB positivity and CSO-PVS across a cohort including healthy controls (both aged over and under 60 years) and patients with CAA-related ICH;

interestingly although those with CAA had a higher burden of CSO-PVS compared with the healthy control groups (p=0.08), there did not appear to be a difference in PiB positivity between healthy older patients and CAA (p=0.53). This may provide further evidence that CSO-PVS burden is a closer correlate of vascular amyloid burden than PiB-PET measures are, but it is difficult to draw firm conclusions as this study included only 31 participants (Charidimou *et al.*, 2015). Additionally, our findings may only be applicable to a selected memory clinic population, specifically those with either AD related cognitive impairment or SVCI, rather than the full spectrum of dementia syndromes. Our project would also have strengthened if participants had other measures of Aβ burden in addition to amyloid-PET, for example quantification of CSF or serum Aβ. Certain measures, for example the ratio of Aβ40:42 (Verbeek *et al.*, 2009), may better capture vascular Aβ and thus might demonstrate with CSO-PVS. It was not possible to draw any conclusions on whether the association between AD diagnosis and CSO-PVS severity was due to any form of CAA. Only small numbers within our cohort had characteristics known to be associated with haemorrhage-associated CAA (type 2), namely an *APOE* ε2 allele (notably, none of the cohort were homozygous for *APOE* ε2), strictly lobar microbleeds and cSS; however, given that over 95% of those with AD have pathological evidence of CAA it may be that the predominant CAA subtype in AD is type 1, which is associated with *APOE* ε4 and capillary level disease (Charidimou *et al.*, 2012). Thus it may be the case that more traditional "haemorrhagic" markers of CAA are of less clinical relevance in this population.

This study provides further supporting evidence that CSO-PVS are a key imaging marker for AD, but without being a measure of amyloid positivity as measured by PiB PET. This raises the possibility that CSO-PVS are a measure of vascular amyloid processes that are not

identified by amyloid-PET, or alternatively of an amyloid independent process, or both. Future work reviewing the association between CSO-PVS and other circulating biomarkers of Aβ burden, and the relationship between tau and CAA will be necessary to further clarify the mechanisms underlying these findings.

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Tables & Figures

Table 1: Baseline characteristics according to disease classification (p values reflect comparisons between ADCI and SVCI groups using Chi-squared, Fishers exact, independent t-tests or Mann-Whitney U tests as appropriate).

	All	ADCI	SVCI	p value
n (%)	226	110 (48.7%)	116 (51.3%)	-
Age, years, mean (SD)	72.1 (8.1)	70.3 (8.8)	73.8 (7.0)	0.0012
Sex, male, n (%)	98 (43.4%)	49 (44.6%)	49 (42.3%)	0.727
Hypertension, n (%)	142 (62.8%)	52 (47.3%)	90 (77.6%)	<0.0001
Diabetes Mellitus, n (%)	45 (19.9%)	15 (13.6%)	30 (25.9%)	0.021
Hyperlipidemia, n (%)	68 (30.1%)	26 (23.6%)	42 (36.2%)	0.039
Prior stroke, n (%)	37 (16.4%)	6 (5.4%)	31 (26.7%)	<0.0001
PiB Positivity, n (%)	120 (53.1%)	86 (78.2%)	34 (29.3%)	<0.0001
Presence of *APOE* ε2, n (%)	22 (10.0%)	7 (6.5%)	15 (13.3%)	0.096
Presence of *APOE* ε3, n (%)	203 (92.3%)	93 (86.9%)	110 (97.4%)	0.004
Presence of *APOE* ε4, n (%)	81 (36.8%)	52 (48.6%)	29 (25.7%)	<0.0001
Lacunes, median (IQR)	1 (0 - 9)	0 (0 - 0)	9 (3.5 - 17)	<0.0001
cSS presence, n (%)	8 (3.5%)	5 (4.6%)	3 (2.6%)	0.426
Strictly lobar CMB (presence), n (%)	17 (7.5%)	7 (6.4%)	10 (8.6%)	0.520
Deep CMB (presence), n (%)	69 (30.8%)	7 (6.5%)	62 (53.5%)	<0.0001
CSO-PVS				
None/Mild (grade 0 - 1), n (%)	73 (32.3%)	16 (14.6%)	57 (49.1%)	<0.0001
Moderate (grade 2), n (%)	91 (40.3%)	49 (44.6%)	42 (36.2%)	
Frequent / Severe (grade 3 - 4), n (%)	62 (27.4%)	45 (40.9%)	17 (14.7%)	
BG-PVS				
None/Mild (grade 0 - 1), n (%)	170 (75.2%)	103 (93.6%)	67 (57.57%)	<0.0001
Moderate (grade 2), n (%)	44 (19.5%)	6 (5.4%)	38 (32.8%)	
Frequent / Severe (grade 3 - 4), n (%)	12 (5.3%)	1 (0.91%)	11 (9.48%)	

Abbreviations:

ADCI Alzheimer's disease related cognitive impairment

APOE Apolipoprotein E

BG Basal ganglia

CSO Centrum semi-ovale

cSS Cortical superficial siderosis

CMB Cerebral microbleed

IQR Interquartile range

PiB 11-Carbon based Pittsburgh compound B

PVS Perivascular space (MRI-visible)

SD Standard deviation

SVCI Subcortical vascular cognitive impairment

Table 2: Logistic regression analysis for predictors of clinical diagnosis (ADCI group)

	Univariable		Multivariable (CSO)		Multivariable (BG)	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
CSO-PVS: None/Mild (grade 0 - 1) Moderate (grade 2) Frequent / Severe (grade 3 - 4)	*Reference Group* 4.16 (2.08 to 8.29) 9.43 (4.29 to 20.71)	<0.00001	*Reference Group* 3.57 (1.17 to 10.89) 6.26 (1.66 to 23.58) ~~5.40 (2.02 to 14.45)~~ ~~7.69 (2.54 to 23.30)~~	~~0.0003~~ 0.017	-	-
BG-PVS: None/Mild (grade 0 - 1) Moderate (grade 2) Frequent / Severe (grade 3 - 4)	*Reference Group* 0.10 (0.04 to 0.26) 0.06 (0.01 to 0.47)	<0.00001	-	-	*Reference Group* 0.26 (0.07 to 1.01) 0.03 (0.00 to 0.44) ~~0.14 (0.04 to 0.45)~~ ~~0.05 (0.00 – 0.53)~~	0.009 ~~0.0004~~
Age (for each year older)	0.95 (0.91 to 0.98)	0.002	0.94 (0.88 to 1.01) ~~0.92 (0.87 to 0.98)~~	0.091 ~~0.006~~	0.95 (0.88 to 1.03) ~~0.93 (0.88 to 0.99)~~	0.214 ~~0.021~~
Hypertension (presence)	0.26 (0.15 to 0.46)	<0.0001	1.13 (0.39 to 3.28) ~~0.78 (0.32 to 1.91)~~	0.828 ~~0.580~~	1.04 (0.35 to 3.11) ~~0.79 (0.32 to 1.93)~~	0.951 ~~0.604~~
Diabetes (presence)	0.45 (0.23 to 0.90)	0.023	0.45 (0.14 to 1.44) ~~0.69 (0.26 to 1.84)~~	0.180 ~~0.457~~	0.42 (0.13 to 1.36) ~~0.79 (0.30 to 2.08)~~	0.149 ~~0.630~~
Hyperlipidaemia (presence)	0.55 (0.31 to 0.97)	0.041	0.39 (0.14 to 1.11) ~~0.42 (0.17 to 1.02)~~	0.077 ~~0.057~~	0.53 (0.18 to 1.55) ~~0.50 (0.21 to 1.19)~~	0.247 ~~0.115~~
Prior stroke (presence)	0.16 (0.06 to 0.40)	<0.0001	0.55 (0.12 to 2.56) ~~0.49 (0.15 to 1.62)~~	0.444 ~~0.245~~	0.53 (0.12 to 2.28) ~~0.47 (0.15 to 1.50)~~	0.396 ~~0.204~~
PiB positivity (presence)	8.64 (4.72 to 15.81)	<0.0001	3.97 (1.46 to 10.80) ~~6.72 (2.83 to 15.96)~~	0.007 ~~<0.0001~~	5.63 (1.96 to 16.21) ~~8.69 (3.53 to 21.39)~~	0.001 ~~<0.0001~~
APOE ε2 (presence)	0.46 (0.18 to 1.17)	0.103	-	-	-	-

APOE ε3 (presence)	0.18 (0.05 to 0.65)	0.009	0.47 (0.05 to 4.31) ~~0.60 (0.10 to 3.66)~~	0.507 ~~0.576~~	0.29 (0.03 to 2.73) ~~0.28 (0.04 to 1.92)~~	0.277 ~~0.193~~
APOE ε4 (presence)	2.73 (1.55 to 4.83)	0.001	0.82 (0.28 to 2.40) ~~1.17 (0.47 to 2.88)~~	0.722 ~~0.739~~	0.65 (0.21 to 1.99) ~~0.89 (0.35 to 2.24)~~	0.449 ~~0.807~~
Lacunes (per additional lacune~~for one number higher~~)	0.49 (0.39 to 0.61)	<0.0001	0.61 (0.48 to 0.78)	<0.0001	0.59 (0.47 to 0.75)	<0.0001
cSS (presence)	1.79 (0.42 to 0.69)	0.432	-	-	-	-
Strictly lobar CMB (presence)	0.72 (0.26 to 1.96)	0.522	-	-	-	-
Deep CMB (presence)	0.06 (0.03 to 0.14)	<0.0001	0.45 (0.11 to 1.75) ~~0.10 (0.03 to 0.27)~~	0.247 ~~<0.0001~~	0.59 (0.14 to 2.54) ~~0.11 (0.04 to 0.32)~~	0.478 ~~<0.0001~~

Table 3: Baseline Characteristics for PiB positive and negative groups (p values reflect comparisons between PiB positive and negative groups using Chi-squared, Fishers exact, independent t-tests or Mann-Whitney U tests as appropriate).

	PiB Negative (retention ratio < 1.5)	**PiB Positive (retention ratio ≥ 1.5)**	**p value**
n (%)	106 (46.9%)	120 (53.1%)	-
Age, years, mean (SD)	72.0 (7.2)	72.2 (8.8)	0.808
Sex, male, n (%)	48 (45.3%)	50 (41.7%)	0.584
Hypertension, n (%)	82 (77.4%)	60 (50.0%)	<0.0001
Diabetes Mellitus, n (%)	27 (25.5%)	18 (15.0%)	0.049
Hyperlipidemia, n (%)	37 (34.9%)	31 (25.8%)	0.138
Prior stroke, n (%)	27 (25.5%)	10 (8.3%)	0.001
ADCI, n (%)	24 (22.6%)	86 (71.7%)	<0.0001
SVCI, n (%)	82 (77.4%)	34 (28.3%)	<0.0001
Presence of *APOE* ε2, n (%)	14 (13.6%)	8 (6.8%)	0.096
Presence of *APOE* ε3, n (%)	102 (99.0%)	101 (86.3%)	<0.0001
Presence of *APOE* ε4, n (%)	18 (17.5%)	63 (53.9%)	<0.0001
WMH volume, ml, median (IQR)	29.9 (13.6 – 45.5)	5.2 (1.2 – 26.2)	<0.00001
Lacunes, median (IQR)	7 (1 – 17)	0 (0 – 2)	<0.00001
cSS presence, n (%)	1 (0.9%)	7 (5.8%)	0.047
Strictly lobar CMB (presence), n (%)	7 (6.6%)	10 (8.3%)	0.623
Deep CMB (presence), n (%)	49 (46.7%)	20 (16.8%)	<0.0001
CSO-PVS			
None/Mild (grade 0 - 1), n (%)	41 (38.7%)	32 (26.7%)	0.033
Moderate (grade 2), n (%)	44 (41.5%)	47 (39.2%)	
Frequent / Severe (grade 3 - 4), n (%)	21 (19.8%)	41 (34.2%)	
BG-PVS			
None/Mild (grade 0 - 1), n (%)	76 (71.7%)	94 (78.3%)	0.480
Moderate (grade 2), n (%)	23 (21.7%)	21 (17.5%)	
Frequent / Severe (grade 3 - 4), n (%)	7 (6.6%)	5 (4.2%)	

Table 4: Logistic regression analysis for predictors of PiB positivity

	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
CSO-PVS: None/Mild (grade 0 - 1) Moderate (grade 2) Frequent / Severe (grade 3 - 4)	*Reference Group* 1.37 (0.74 to 2.54) 2.50 (1.24 to 5.04)	0.032	*Reference Group* 0.67 (0.29 to 1.59) 0.93 (0.35 to 2.46)	0.607
BG-PVS: None/Mild (grade 0 - 1) Moderate (grade 2) Frequent / Severe (grade 3 - 4)	*Reference Group* 0.74 (0.38 to 1.43) 0.58 (0.18 to 1.89)	0.480	-	-
Hypertension (presence)	0.29 (0.16 to 0.52)	<0.0001	0.52 (0.24 to 1.10)	0.085
Diabetes (presence)	0.52 (0.27 to 1.00)	0.051	0.97 (0.42 to 2.26)	0.947
Previous stroke (presence)	0.27 (0.12 to 0.58)	0.001	0.48 (0.17 to 1.33)	0.157
ADCI diagnosis	8.64 (4.72 to 15.81)	<0.0001	7.56 (2.59 to 22.46)	<0.0001
APOE ε2 (presence)	0.47 (0.19 to 1.16)	0.102		
APOE ε3 (presence)	0.06 (0.01 to 0.48)	0.007	0.25 (0.03 to 2.29)	0.221
APOE ε4 (presence)	5.51 (2.95 to 10.29)	<0.0001	3.87 (1.80 to 8.32)	0.001
WMH volume (for each ml higher)	0.97 (0.96 to 0.98)	<0.0001	1.03 (1.00 to 1.05)	0.055
Lacunes (for one number higher)	0.88 (0.83 to 0.92)	<0.0001	0.94 (0.88 to 0.99)	0.026
cSS (presence)	6.50 (0.79 to 53.76)	0.082	-	-
Strictly lobar CMB (presence)	1.29 (0.47 to 3.51)	0.623	-	-
Deep CMB (presence)	0.23 (0.12 to 0.43)	<0.0001	1.07 (0.43 to 2.65)	0.886

Figure 1: Examples of MRI-visible perivascular spaces.

[A - C] Examples of MRI-visible CSO-PVS, [A] None/Mild grade, [B] Moderate grade, [C] Frequent/Severe grade

[D - F] Examples of MRI-visible BG-PVS, [D] None/Mild grade, [E] Moderate grade, [F] Frequent/Severe grade

Figure now included as separate TIFF file, as per author instructions.