ORIGINAL RESEARCH

Topography and Determinants of Magnetic Resonance Imaging (MRI)-Visible Perivascular Spaces in a Large Memory Clinic Cohort

Sara Shams, MD, PhD; Juha Martola, MD, PhD; Andreas Charidimou, MD, PhD; Mykol Larvie, MD, PhD; Tobias Granberg, MD, PhD; Mana Shams, BS; Maria Kristoffersen-Wiberg, MD, PhD; Lars-Olof Wahlund, MD, PhD

***Background*—**Magnetic resonance imaging-visible perivascular spaces (PVS) are related to interstitial fluid clearance pathways (including amyloid-β) in the brain and are suggested to be a marker of cerebral small vessel disease. We investigated the role, topography, and possible implications of PVS in cognitive impairment.

***Methods and Results*—**A total of 1504 patients undergoing memory clinic investigation and an associated brain magnetic resonance imaging scan were included in this cross-sectional study. Magnetic resonance images were assessed for markers of small vessel disease. Additionally, 1039 patients had cerebrospinal fluid analysis of amyloid-β 42, total tau (T-tau), and phosphorylated tau (*P*-tau); 520 patients had apoE genotyping done. Results were analyzed with generalized linear models. A total of 289 (19%; 95% confidence interval, 17–21) had a high-grade PVS in the centrum semiovale (CSO) and 65 (4%; 95% confidence interval: 3%–5%) in the basal ganglia (BG). Centrum semiovale– and BG-PVS were both associated with high age ($P<0.001$), hypertension ($P<0.001$), probable cerebral amyloid angiopathy ($P<0.05$), moderate-to-severe white matter hyperintensities ($P<0.001$), cortical superficial siderosis ($P<0.001$), cerebral microbleeds ($P<0.001$), and PVS. centrum semiovale–PVS was separately associated with strictly lobar cerebral microbleeds ($P=0.057$). BG-PVS was associated with strictly deep cerebral microbleeds ($P<0.001$), lacunes ($P<0.001$), and vascular dementia ($P=0.04$). BG-PVS showed a tendency to be associated with high cerebrospinal fluid tau (B=0.002, $P=0.04$) in the whole cohort and in Alzheimer's disease (B=0.005; $P=0.02$). No other associations with cerebrospinal fluid or the apoE e4 allele was observed.

***Conclusions*—**Centrum semiovale–PVS and BG-PVS have different underlying etiology, being associated with cerebral amyloid angiopathy and hypertensive vasculopathy, respectively, although a significant overlap between these pathologies is likely to exist.
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Key Words: cerebral microbleed • cerebral small vessel disease • cognitive impairment • magnetic resonance imaging

MRI-visible perivascular spaces (PVS; commonly known as Virchow-Robin spaces) have previously been considered a normal finding in the aging brain and hence overlooked. However, accumulating data have come to challenge this established view.

PVS are interstitial fluid-filled channels, surrounding arterioles entering the brain.[1] Recently, PVS have been suggested to be part of the brain's intrinsic lymphatic system, dubbed the glymphatic system.[2] Interstitial fluid and solutes, including amyloid, is thought to be transported in the PVS,[3,4] and thus, PVS when enlarged or visible on MRI, may be a marker of decreased amyloid clearance. This is of special significance in cerebral amyloid angiopathy (CAA) and cognitive impairment, where decreased amyloid clearance plays a significant role in the disease processes.

Previous studies have shown that increased number of PVS on MRI show associations with high age, impaired cognitive function, other MRI markers of small vessel disease, and spontaneous intracerebral hemorrhage (ICH).[5] Associations have shown to vary depending on localization, with PVS in the centrum semiovale (CSO) being associated with markers of CAA, and PVS in the basal ganglia (BG) showing associations with markers indicative of hypertensive vasculopathy.[5–8]

From the Division of Medical Imaging and Technology, Departments of Clinical Science, Intervention, and Technology (S.S., J.M., T.G., M.S., M.K.-W.) and Neurobiology (L.-O.W.), Karolinska Institutet, Stockholm, Sweden; Department of Radiology (S.S., J.M., T.G., M.S., M.K.-W.) and Division of Clinical Geriatrics (L.-O.W.), Karolinska University Hospital, Stockholm, Sweden; Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston, MA (A.C.); Department of Radiology, Massachusetts General Hospital, Boston, MA (M.L.).

Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/6/9/e006279/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Sara Shams, MD, PhD, Department of Radiology, Karolinska University Hospital, SE-14186 Stockholm, Sweden. E-mail: sara.shams@ki.se

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Clinical Perspective

What Is New?

- Enlarged perivascular spaces are a marker of small vessel disease, and the distribution reflects the underlying etiology.

What Are the Clinical Implications?

- Enlarged perivascular spaces may be a new marker to analyze clinically with regard to the assessment of small vessel disease and cognitive impairment; future research will elucidate the importance of this marker.

In cognitive impairment, PVS may represent CAA and be a new marker to consider, of value in routine brain MRI interpretations. In this study, we sought to explore PVS as a possible pathological finding in cognitive impairment and investigate the clinical value of PVS in cognitive impairment. We investigated risk factors for high-degree PVS in the CSO and basal ganglia (BG) in a large, unselected memory clinic population.

Material and Methods

Patients

This is a cross-sectional study, part of the KIDS (Karolinska Imaging Dementia Study), a series of studies on small vessel disease and the impact in cognitive impairment. A total of 1509 consecutive patients, undergoing memory investigations and an accompanying MRI brain scan, were recruited from January 1, 2006 to January 1, 2012, with sample size based on past power calculations. The population was mainly white.

Exclusion criteria consisted of insufficient scan quality and a history of traumatic brain injury; after exclusion, 1504 patients remained. Diagnoses, according to the International Classification of Diseases, Tenth Revision criteria, were established in multidisciplinary conferences with consideration of all data. Clinical parameters were recorded in patient notes and assessed in our study. The diagnostic groups and accompanying International Classification of Diseases codes for this study are seen in Table S1.[9] Additionally, we classified patients into probable CAA or not, using a modified version of the Boston criteria,[10] with cerebral microbleeds (CMBs) instead of ICH. Informed consent was obtained from each patient, according to the Declaration of Helsinki, and ethical approval was obtained from the regional ethical board, Stockholm, Sweden.

MRI Protocol

All patients were scanned at the Radiology Department, Karolinska University Hospital (Stockholm, Sweden), on three 1.5 and 3.0 Tesla MRI scanners (Siemens Medical Systems, Erlangen, Germany). Distribution of patients on the 3 scanners was made based on clinical availability. Full protocols, with conventional sequences such as T1, T2, and fluid-attenuated inversion recovery, as well as axial hemosiderin sequences T2* and/or susceptibility weighted imaging were used for all patients. MRI data are detailed in Table S2.

Image Analysis

All MR images were assessed on a radiological PACS workstation, in consensus, by 2 raters, a senior neuroradiologist (J.M.) and a trained MD (S.S.). Image assessments were done according to the recently proposed STRIVE v1 (STandards for ReportIng Vascular changes on nEuroimaging).[11] Both raters were blinded to all patient data. PVS were rated on axial T2 sequences, in the CSO and BG, and rated into 0=none, 1=1 to 10, 2=11 to 20, 3=21 to 40, or 4=>40, according to the validated PVS rating scale.[1,7,12] PVS score was first rated individually by the raters, and if scores were differing between the raters, the final PVS score was settled through consensus. CMBs were rated on axial T2* and/or susceptibility weighted imaging according to the Microbleed Anatomical Rating Scale,[13] with minor modifications, as previously described in detail.[14] White matter hyperintensities were rated according to the Fazekas scale from 0 to 3 (none or single punctate; multiple punctate; early confluent; or confluent).[15] Lacunes were defined as 3 to 15 mm of size, with cerebrospinal fluid (CSF) signal on fluid-attenuated inversion recovery, T2, and T1. Cortical superficial siderosis was defined as linear gyriform hypointensities.[16]

APOE Genotyping and CSF Analysis

APOE genotyping, through polymerase chain reaction, was performed for a subset of patients (n=520) on coded genomic DNA samples. CSF samples were obtained by lumbar puncture and were available for 1039 patients, and the procedure of analysis has been described elsewhere.[17,18] CSF was analyzed for amyloid β 42 (Innotest β-Amyloid(1-42)), total tau (T-tau) (Innotest hTau-Ag), and tau phosphorylated at threonine 181 (*P*-tau) (Innotest Phospho-tau(181P); Innogenetics, Ghent, Belgium). CSF/serum albumin ratios, as a marker of blood–brain barrier integrity, were calculated by blood sampling at the same visit as the lumbar puncture. The unit used for biomarkers is ng/L. All analysis was done blinded to the study hypothesis and all clinical data, at the Department of Clinical Chemistry, Karolinska University Hospital.

Statistical Analysis

We prespecified a dichotomized classification of PVS degree as high (score >2) or low (score ≤2). This definition is in line

with the most severe category of CSO-PVS used in previous studies (and found to relate to vascular risk factors) and appears to be sensitive for CAA diagnosis.[5,6,19,20] Inter-rater agreement was assessed with kappa statistics. We compared demographic, clinical, and imaging characteristics of our memory clinic patients with high versus low CSO-PVS degree and high versus low BG-PVS degree using appropriate univariable tests: chi-square test or Fisher's exact test for categorical variables and Student *t* test/Mann–Whitney *U* tests for age and other continuous variables. Uni- and multivariable logistic regression analyses were used to explore the relation between high CSO-PVS degree and high BG-PVS degree, in separate models, without interaction terms. We adjusted our multivariable models for diagnostic groups and MRI parameters (field strength, ie, 1.5 versus 3 Tesla and susceptibility weighted imaging versus T2* gradient recalled echo). We repeated these analyses in patients with mild cognitive impairment and Alzheimer's disease and in patients classified as probable CAA, based on the Boston criteria.

The association between PVS and CSF biomarkers was investigated with logistic regression analysis. PVS dichotomized was used as a dependent variable with CSF biomarkers as independent variables in the model. The significance level was set at 0.05, equaling 0.02 after correction for multiple comparisons, according to the Benjamini–Hochberg procedure.[21] Stata (version 13.0; StataCorp LP, College Station, TX) and SPSS software (version 22.0; SPSS, Inc., Chicago, IL) were used.

Results

Patient demographics are seen in Table 1. High-grade CSO-PVS (ie, a score >2) was detected in 289 of 1504 patients (19%; 95% confidence interval [CI], 17–21) and high-grade BG-PVS in 65 of 1504 (4%; 95% CI, 3–5) patients. Inter-rater agreement for PVS equaled excellent agreement (0.9, kappa value). Figure 1 shows examples of CSO- and BG-PVS. High-grade CSO- and BG-PVS were most common in patients with probable CAA, followed by vascular dementia, Alzheimer's disease, and mild and subjective cognitive impairment (Table 1). Presence of high-grade CSO- ($P<0.001$) and BG-PVS ($P=0.01$) varied significantly across diagnostic groups. Clinical associations are detailed in Table 1.

PVS degree varied according to the presence of strictly deep or lobar CMBs (Figure 2). Patients with lobar CMBs had

Table 1. Descriptive Patient Demographics Across Different Cognitive Impairment Diagnostic Groups and PVS Prevalence

	CSO-PVS >20 (n=289)	CSO-PVS <20 (n=1215)	*P* Value	BG-PVS>20 (n=65)	BG-PVS<20 (n=1439)	*P* Value
Age, y, mean (±SD)	66 (±8)	62(±10)	<0.001	72 (±9)	63 (±10)	<0.001
Male, n (%)	142 (49)	565 (47)	0.413	38 (58)	669 (46)	0.058
MMSE score, mean (±SD)	25 (±4)	25 (±5)	0.462	23 (±5)	25 (±5)	0.001
Hypertension	132 (46)	410 (34)	<0.001	41 (63)	501 (35)	<0.001
Hyperlipidemia	72 (25)	217 (18)	0.006	23 (35)	266 (18)	0.001
Diabetes mellitus	29 (10)	118 (10)	0.854	11 (17)	136 (9)	0.047
ApoE e4	61 (21)	194 (16)	0.262	14 (22)	241 (17)	0.787
CMBs	94 (33)	238 (20)	<0.001	42 (65)	290 (20)	<0.001
Moderate-to-severe WMH presence	84 (29)	149 (12)	<0.001	34 (52)	199 (14)	<0.001
Lacunes	76 (26)	135 (11)	<0.001	36 (55)	175 (12)	<0.001
Siderosis	21 (7)	21 (2)	<0.001	10 (15)	32 (2)	<0.001
3.0T MRI imaging	98 (34)	272 (22)	<0.001	17 (26)	353 (25)	0.764

	CSO-PVS >20 (n=289)	BG-PVS>20 (n=65)
Alzheimer's disease (n=423), n (%; 95% CI)	90 (21; 95 CI, 18–25)	23 (5; 95% CI, 4–8)
Mild cognitive impairment (n=418), n (%, 95% CI)	93 (22; 95% CI, 19–26)	24 (6; 95% CI, 4–8)
Subjective cognitive impairment (n=385), n (%, 95% CI)	48 (12; 95% CI, 10–16)	5 (1; 95% CI, 0.5–3.0)
Vascular dementia (n=54), n (%, 95% CI)	16 (30; 95% CI, 19–43)	4 (7; 95% CI, 3–18)
Probable CAA (n=98), n (%, 95% CI)	29 (30; 95% CI, 24–36)	6 (9; 95% CI, 3–15)

BG indicates basal ganglia; CAA, cerebral amyloid angiopathy; CI, confidence interval; CSO, centrum semiovale; ; MMSE, Mini–Mental State Examination; PVS, perivascular spaces; WMH, white matter hyperintensities.

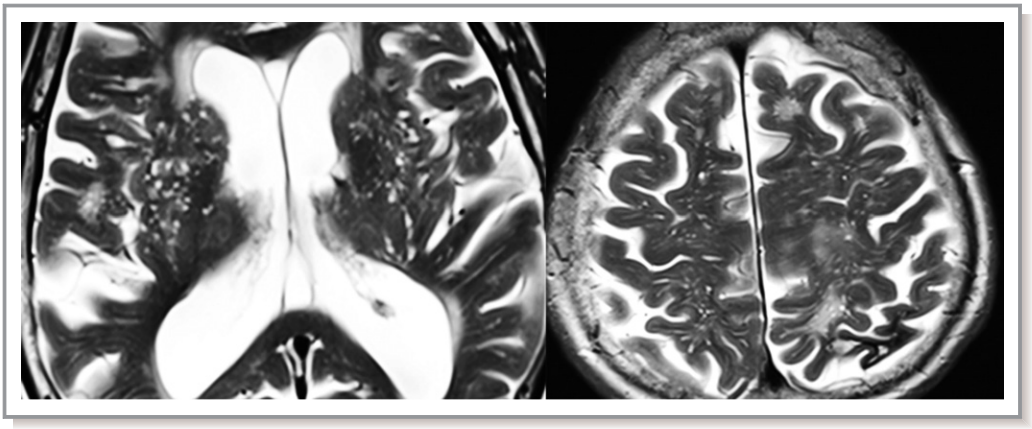

Figure 1. Enlarged perivascular spaces in the basal ganglia and centrum semiovale, respectively.

a higher mean rating of CSO-PVS (2.1±0.9 versus 1.7±0.8; $P<0.001$) and BG-PVS (1.2 ±0.5 versus 1.6±0.7; $P<0.001$), compared with patients without CMBs. The same was true for patients with deep CMBs, having a higher rating of CSO-PVS (2.1±0.9 versus 1.8±0.8; $P<0.001$) and BG-PVS (1.9±0.8 versus 1.3±0.5; $P<0.001$).

Demographic, Clinical, and Neuroimaging Findings and Predictors of PVS

Univariable, controlled, logistic regression analysis of demographic, clinical, and imaging characteristics between patients with versus without high-grade CSO-PVS and

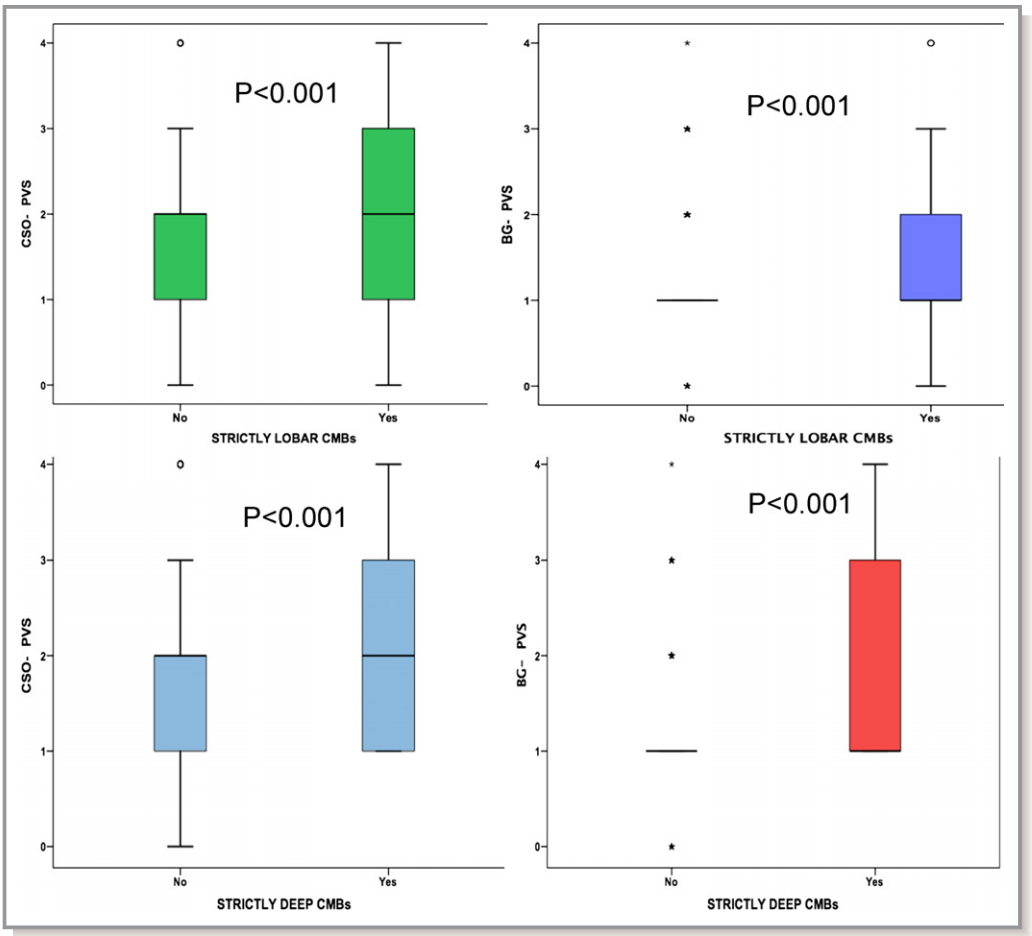

Figure 2. Distribution of PVS in patients with strictly lobar and strictly deep CMBs. The y-axis represents the ordinal rating scale, 0=0 PVS, 1=1 to 10, 2=11 to 20, 3=21 to 40, and 4=>40. BG indicates basal ganglia; CSO, centrum semiovale; PVS, enlarged perivascular spaces.

BG-PVS are shown in Table 2. In summary, it was observed that high-grade CSO-PVS and BG-PVS both were associated with high age, hypertension, probable CAA, high burden of white matter hyperintensities, CMBs, and cortical superficial siderosis. BG-PVS was additionally associated with diabetes mellitus, hyperlipidemia, vascular dementia, and lacunes (Table 2).

Controlled multivariable logistic regression analyses were constructed based on significant variables in Table 2. In the whole cohort, associations with high-grade CSO- and BG-PVS were observed with high age, high burden of white matter hyperintensities, cortical superficial siderosis, and PVS. High-grade BG-PVS was additionally associated with hypertension, lacunes, and strictly deep CMBs. Associations were further analyzed in Alzheimer's disease and mild cognitive impairment jointly, as well as in patients with probable CAA, using only imaging manifestations of small vessel disease because of to the sample size (n=98; Table 3).

CSF Biomarkers and PVS

In the whole cohort, low CSF amyloid β 42 showed a tendency to be associated with high-grade CSO-PVS (B=−0.001; *P*=0.03). High numbers of BG-PVS showed a tendency to be associated with high tau (B=0.002; *P*=0.04), in the whole cohort, and in Alzheimer's disease (B=0.005; *P*=0.02). High-grade PVS in the CSO and BG in mild cognitive impairment, subjective cognitive impairment, vascular dementia, and probable-CAA did not show any associations with CSF biomarkers.

Discussion

In this large, cross-sectional memory cohort, we principally show that: (1) High-grade PVS is common in a memory clinic and most frequent in vascular dementia and patients classified as probable CAA. (2) CSO-PVS and BG-PVS show

Table 2. Associations of Potential Risk Factors With High Degree of PVS Stratified by Location, Regression Analyses

	High (>20) CSO-PVS grade (n=289), OR (95% CI)	High (>20) BG-PVS grade (n=65), OR (95% CI)
Age >65 y	2.2 (1.6–3.1), *P*<0.0001	5.9 (3.0–11.4), *P*<0.0001
Sex, male	1.0 (0.7–1.3), *P*=0.821	1.5 (0.9–2.6), *P*=0.153
Hypertension, presence	1.4 (1.1–2.0), *P*=0.01	2.9 (1.7–5.2), *P*<0.0001
Diabetes mellitus, presence	1.5 (0.8–2.8), *P*=0.355	2.1 (1.0–4.4), *P*=0.06
Hyperlipidemia, presence	1.3 (0.9–1.9), *P*=0.25	2.2 (1.2–3.8), *P*=0.009
Smoking	0.9 (0.5–1.4), *P*=0.899	1.6 (0.7–3.6), *P*=0.246
MMSE <21	0.8 (0.5–1.2), *P*=0.557	0.7 (0.3–1.6), *P*=0.455
ApoE e4	1.2 (0.7–2.0), *P*=0.470	0.8 (0.4–1.9), *P*=0.660
ApoE e4/4	1.4 (0.7–3.9), *P*=0.310	0.4 (0.1–1.5), *P*=0.166
Alzheimer's disease	1.0 (0.6–1.7), *P*=0.943	3.2 (0.4–25.6), *P*=0.280
Mild cognitive impairment	1.2 (0.7–2.2), *P*=0.462	4.7 (0.6–39.3), *P*=0.15
Vascular dementia	1.3 (0.6–2.9), *P*=0.502	11.1 (1.1–112.2), *P*=0.04
Probable CAA	1.8 (1.0–3.1), *P*=0.03	3.2 (1.2–8.9), *P*=0.02
Lacune, presence	2.7 (1.8–3.9), *P*=0.749	8.2 (4.6–14.5), *P*<0.0001
Moderate-to-severe WMH, presence	3.7 (2.5–5.4), *P*<0.0001	8.3 (4.5–15.7), *P*<0.0001
Probable CAA (vs no CMBs)	1.0 (0.9–1.1), *P*=0.968	3.1 (1.2–8.0), *P*=0.02
Strictly deep CMBs	3.7 (2.1–6.2), *P*<0.0001	12.7 (6.7–24.0), *P*<0.001
Strictly lobar CMBs	2.1 (1.4–3.0), *P*<0.001	4.6 (2.5–8.1), *P*<0.001
CMB presence	1.9 (1.3–2.6), *P*<0.0001	7.0 (3.9–12.4), *P*<0.0001
High (>20) BG-PVS grade	5.7 (3.2–9.9), *P*<0.001	…
High (>20) CS-PVS grade	…	5.7 (3.2–10.9), *P*<0.0001
Cortical superficial siderosis	5.4 (2.6–10.4), *P*<0.0001	5.8 (2.5–13.6), *P*<0.0001

BG indicates basal ganglia; CAA, cerebral amyloid angiopathy; CI, confidence interval; CMBs, cerebral microbleeds; CSO, centrum semiovale; MMSE, Mini–Mental State Examination; OR, odds ratio; PVS, perivascular spaces; WMH, white matter hyperintensities.

Table 3. Associations of High (>20) CSO-PVS Grade and High (>20) BG-PVS Grade in Different Multivariable Logistic Regression Models

	High (>20) CSO-PVS Grade (OR; 95% CI)	High (>20) BG-PVS Grade (OR; 95% CI)
Whole cohort		
Age, per y increase	1.03 (1.01–1.05); *P*=0.0001	1.07 (1.03–1.11); *P*<0.0001
Hypertension, presence	1.00 (0.70–1.40); *P*=0.949	2.00 (0.98–3.4); *P*=0.059
Hyperlipidemia, presence	…	1.20 (0.59–2.44); *P*=0.607
Moderate-to-severe WMH, presence	1.84 (1.30–2.70); *P*=0.002	2.85 (1.46–5.57); *P*=0.002
Lacunes	…	3.8 (2.0–7.3); *P*<0.001
Strictly lobar CMBs	1.40 (0.99–2.15); *P*=0.057	0.99 (0.46–3.97); *P*=0.157
Strictly deep CMBs	1.7 (0.62–4.41); *P*=0.312	6.8 (2.2–20.9); *P*<0.0001
Cortical superficial siderosis	2.1 (1.03–4.23), *P*=0.03	2.6 (1.0–7.1), *P*=0.05
High (>20) BG-PVS grade	2.85 (1.62–4.99); *P*=0.001	…
High (>20) CSO-PVS grade	…	3.16 (1.7–5.9); *P*<0.0001
Alzheimer's disease and MCI		
Age, per y increase	1.0 (1.0–1.1), *P*=0.400	1.1 (1.1–1.2), *P*<0.001
Hypertension, presence	1.1 (0.8–1.6), *P*=0.598	2.5 (1.1–5.7), *P*=0.03
Hyperlipidemia, presence	…	1.2 (0.5–2.8), *P*=0.414
Moderate-to-severe WMH, presence	2.5 (1.6–3.9), *P*<0.001	2.3 (1.1–5.0), *P*=0.03
Lacunes	…	3.3 (1.5–7.0), *P*<0.001
Strictly lobar CMBs	0.9 (0.5–1.5), *P*=0.637	1.3 (0.6–3.0), *P*=0.492
Strictly deep CMBs	1.3 (0.4–4.3), *P*=0.697	11.7 (3.2–43.4), *P*<0.001
Cortical superficial siderosis	4.4 (1.9–10.4), *P*<0.001	2.6 (0.8–8.4), *P*=0.458
High (>20) BG-PVS grade	2.4 (1.2–5.1), *P*=0.02	…
High (>20) CSO-PVS grade	…	3.1 (1.5–6.6), *P*=0.006
Probable CAA		
Age	1.1 (1.0–1.1); *P*=0.06	1.0 (0.9–1.2); *P*=0.774
Moderate-to-severe WMH, presence	2.1 (0.8–6.0), *P*=0.151	1.5 (0.3–9.0); *P*=0.717
Lacunes	…	0.8 (0.1–5.6); *P*=0.877
Cortical superficial siderosis	7.8 (1.9–30.6), *P*=0.004	1.3 (0.3–8.9), *P*=0.581
High (>20) BG-PVS grade	1.1 (0.2–7.0), *P*=0.921	…
High (>20) CSO-PVS grade	…	1.1 (0.2–7.5); *P*=0.946

Both models are further adjusted for MRI parameters, including magnetic field strength (1.5 Tesla [T] vs 3T) and susceptibility weighted imaging vs T2* gradient recalled echo, and in the case of whole cohort also for diagnosis. BG indicates basal ganglia; CAA, cerebral amyloid angiopathy; CI, confidence interval; CMBs, cerebral microbleeds; CSO, centrum semiovale; MCI, mild cognitive impairment; OR, odds ratio; PVS, perivascular spaces; WMH, white matter hyperintensities.

topographical associations depending on underlying small vessel disease etiology, that is, CAA and hypertensive vasculopathy, respectively, although our data suggest an overlap between these 2 pathologies. (3) High tau levels in the CSF, as a marker of neurodegeneration, show a tendency to be associated with BG-PVS.

There are few previous studies on MRI-visible PVS, with the use of validated rating scales, in memory clinic cohorts. High-grade white matter PVS has shown a similar prevalence to ours, 25%, and BG-PVS 10%, in a memory clinic cohort,[22] although using a different rating scale. Patients with Alzheimer's disease have further shown a higher degree of PVS compared with normal controls,[23] which is in harmony with our results. BG-PVS has shown to be higher in patients with vascular dementia when compared with Alzheimer's disease or healthy controls, with CSO-PVS not showing any differences across groups.[24] This is similar to our results, albeit CSO- and BG-PVS varied significantly across diagnoses.

In patients with ICH, prevalence of severe PVS has shown to be 36% in the CSO, in patients with strictly lobar ICH (probable or possible CAA), and 18% in patients with other ICH.[5] Prevalence of high-grade CSO-PVS in patients with CAA

is around 61%[19] and varies strongly depending on whether or not patients have CAA. Patients with histology verified that CAA had a 86% prevalence of high-grade CSO-PVS versus 0% in patients without CAA.[25] Inclusion of CSO-PVS in the Boston criteria for CAA has shown to improve the sensitivity from 77% to 92%.[25]

Our study adds support to the existing framework that distribution of PVS may vary according to underlying small vessel disease etiology, CSO-PVS being mainly associated with CAA, and hypertensive vasculopathy mainly with BG-PVS. In our cohort, CSO-PVS showed associations with strictly lobar CMBs as well as cortical superficial siderosis, both suggested to be sensitive markers of CAA. BG-PVS was associated with cortical superficial siderosis as well as with strictly deep CMBs, lacunes, and hypertension, suggesting that BG-PVS is more associated with hypertensive vasculopathy, even though an overlap with CAA pathology exists. The number of variables associated with both CSO- and BG-PVS suggest a significant overlap between CAA and hypertensive vasculopathy in our cohort. Past memory clinic data have similarly shown associations between lobar CMBs and CSO-PVS, and hypertension and BG-PVS.[22]

PVS explored in different populations have shown similar topographical associations. In patients with ICH, associations have been observed between BG-PVS and age, white matter hyperintensities, and deep CMBs; CSO-PVS has shown associations with age[5] and subacute diffusion weighted imaging lesions.[26] PVS in the white matter has shown associations to a more-posterior location of white matter hyperintensities,[27] which may be more typical for CAA. In lacunar stroke patients, BG-PVS, but not CSO-PVS, has shown associations to progression of white matter hyperintensities.[28] Cortical superficial siderosis has shown a strong association with CSO-PVS, but not BG-PVS, in a cohort with probable/possible CAA, as well as with both types of PVS, in memory clinic cohorts.[9,19,29] Larger PVS volume in the white matter has also been shown in males when compared with women.[23] In patients with acute stroke, associations have been observed between BG-PVS and high age, CSO-PVS, atrophy, and lacunar stroke subtype.[30] Past data corroborate our finding that CSO-PVS is related to CAA and BG-PVS to hypertensive vasculopathy, with overlap between the 2 pathologies.

PVS may also be viewed as a third space of atrophy in the brain. This may be attributed to neurodegeneration, given that in our cohort, or because small vessel disease caused atrophy, that manifests in the same location as the specific small vessel disease. BG-PVS, but not CSO-PVS, has shown associations with atrophy.[30,31] Further studies need to investigate different forms of brain atrophy and relations with PVS.

Associations between PVS and CSF biomarkers as well as the apoE e4 allele are largely uninvestigated previously in patients with cognitive impairment. In our study, tendencies for high BG-PVS to be associated with high CSF tau were observed. No association with the apoE e4 allele was noted. In population-based studies without dementia, no association between PVS and amyloid β 42 and amyloid β 40 has been noted.[32] In a smaller study on 7 Tesla in 5 patients with CAA and Alzheimer's pathology in autopsy, an association between PVS and higher CAA cortical score was noted.[33] No association was observed between PVS and amyloid plaques, or CAA-related vasculopathy.[33] In probable CAA patients and healthy controls, Pittsburgh compound B binding in the cortex was higher with increased CSO-PVS.[20]

Limitations in our study include the use of 1.5 to 3.0 Tesla scanners, which, however, were corrected for in our analyses. Moreover, no study has investigated whether and to what extent PVS scores vary within these different field strengths. Another limitation is the fact that diagnoses may be biased by circular reasoning. Diagnoses were set clinically in a multidisciplinary setting, utilizing both clinical data and neuroradiological assessment, which may have affected patients classified as vascular dementia. The clinical group was, however, not aware of the hypotheses of this and other studies on small vessel disease. Strengths in our study include a large and diverse cohort, with CSF data, and rigorous rating with the use of a validated scale.

Conclusion

We conclude that high-grade PVS is common in a memory clinic, and that it shows regional preferences, with CSO-PVS mostly associated with CAA, and BG-PVS with hypertensive vasculopathy, with a possible significant overlap between these 2 pathologies.

Author Contributions

S. Shams: study concept and design, image analysis, data acquisition and analysis, drafting of manuscript and critical revision; S. Shams is guarantor. Martola: study design, image analysis, critical revision of manuscript. Charidimou: study concept and design, data analysis, drafting of manuscript and critical revision. Granberg: data acquisition, critical revision of manuscript. M. Shams: data acquisition and analysis, critical revision of manuscript. Kristoffersen Wiberg: MRI logistics, critical revision of manuscript. Wahlund: patient enrollment, critical revision of manuscript.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Diagnostic groups and accompanying ICD-codes for this study

Diagnosis (n=1504)	**ICD-code**
Alzheimer's Disease (n=423)	F00.0 (early onset, n=176), F00.1 (late onset, n=146), F00.2 (atypical disease with vascular components, n=96), F00.9 (unspecified Alzheimer's disease, n=5)
Mild Cognitive Impairment (n=418)	F06.7
Subjective Cognitive Impairment (n=385)	Z03.2A, Z03.3 and R41.8A
Vascular Dementia (n=54)	F01.1, F01.2, F01.3, F01.9 and CADASIL (4 patients) based on I63.8
Other Dementias (n=126)	Alcohol Related Dementia (n=20) (F10.6, F10.7a), Frontotemporal Lobe Dementia (n=30) (F0.70, F02.0), Parkinson's Dementia (n=21) (F02.3, G31.8a), Unspecified Dementia (n=55) (F03.9)
Other Disorders (n=98)	Asymptomatic Hereditary Dementia (n=45) (Z31.5), Other Disorders (n=53) (Depression, hallucination, delirium, other reactions to severe stress, psychosis, bipolar disease, amnesia, systemic lupus erythematosus encephalopathy, dysphasia, degenerative diseases in the basal ganglia, hydrocephalus, narcolepsia, Creutzfeldt Jacob disease, supratentorial epidermoid tumour, cerebral infarctions, anemia, hereditary ataxia, multiple system degeneration and progressive supranuclear palsy.)

Table S2. MRI parameters.

Siemens Magnetom		Symphony	Avanto	Trio
Field strength (T)		1.5	1.5	3.0
T2*	TE	25	26	20
	TR	792	800	620
	FA	20°	20°	20°
	ST	5.0	5.0	4.0
SWI	TE	-	40	20
	TR	-	49	28
	FA	-	15°	15°
	ST	-	4.0	1.6
T2	TE	92	94	93
	TR	5000	4200	6000
	FA	150	150	120
	ST	5.0	5.0	4.00

TE = Time to echo (ms), TR = Time to repeat(ms), FA = Flip angle (°), ST = Slice thickness (mm)