Markers of Aβ deposition and burden of enlarged perivascular spaces in patients with cognitive impairment and small vessel disease.

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Abstract

MRI-visible enlarged perivascular spaces (EPVS) are common in patients with cognitive impairment and possibly linked to Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA). In a study of memory clinic patients (n=450; mean age 66.5±7.45, 45.8% female), we investigated CSF Aβ1-42 (AD biomarker) and strictly lobar microbleeds (CAA marker) in relation to centrum semiovale EPVS (CSO-EPVS). Age-controlled analyses showed that severe CSO-EPVS associated with Aβ status (odds ratio [OR]=1.51, 95%CI=1.02-2.24), but not strictly lobar microbleeds (OR=1.39, 95%CI=0.92-2.11), with no significant Aβ status and microbleeds interaction. This implies that in this setting, severe CSO-EPVS is not a specific indicator of CAA.

Keywords: perivascular spaces, Aβ accumulation, cerebral amyloid angiopathy, strictly lobar microbleeds, memory clinic, small vessel disease

Introduction

MRI-visible enlarged perivascular spaces (EPVS) are a common imaging finding in patients with cognitive impairment [1,2] and are recognized as a marker of cerebral small vessel disease (SVD) [3,4]. Although the exact underlying mechanisms remain unclear, widening of EPVS has been linked to the dysfunction of interstitial fluid clearance pathways[5]. Emerging research highlighting the role of the glymphatic system in the clearance of amyloid beta (Aβ) in Alzheimer's disease (AD) [6] could imply a link between AD and EPVS burden. However, previous studies have yielded inconsistent findings regarding the association between EPVS burden and markers of parenchymal Aβ accumulation in AD[7–9]. Another condition associated with cognitive impairment and characterized by Aβ accumulation is cerebral amyloid angiopathy (CAA). Notably, there is a growing body of literature linking CAA to the presence of severe EPVS burden, particularly in the centrum semiovale (CSO-EPVS) [10–14]. Consequently, severe CSO-EPVS has been proposed as a diagnostic marker for CAA [7,13] and is now included in the Boston criteria v2.0 for CAA[15].

Given the frequent co-occurrence of AD and CAA in individuals with cognitive impairment[16], the presence of CAA may further increase CSO-EPVS burden in patients with AD. This has possible implications for diagnosis and management of patients, particularly due to the increased risk of intracerebral hemorrhage associated with CAA[17]. Therefore, the aim of this study was to investigate the association of markers of AD and CAA pathology, both individually and in interaction, with severe CSO-EPVS in a cohort of patients enriched for small vessel disease (SVD) presenting in a memory clinic.

Methods

We selected patients from the TRACE-VCI cohort [18] which consisted of 860 consecutive individuals presenting with cognitive complaints in a memory clinic. To be included in the cohort, participants needed to demonstrate evidence of at least one form of vascular brain injury on MRI: white matter hyperintensities rated on Fazekas scale ≥ 2, lacunar infarct, non-lacunar infarct, cerebral microbleed, intracerebral hemorrhage or a Fazekas scale grade 1

with the presence of two or more vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, obesity, current smoking, or a history of a vascular event other than stroke). Detailed information on the inclusion and exclusion criteria, as well as the study's design and methodological protocols, have been previously reported[18]. The study received approval from the local institutional review boards, and all participants provided written informed consent.

For the present analyses, we selected patients that had both available cerebrospinal fluid (CSF) AD biomarkers (unavailable for 318 patients) and MRI data. We excluded eight patients due to unavailable or low-quality MRI data for EPVS rating, as well as 81 patients with mixed cerebral microbleeds. This resulted in a final sample of 450 patients for our primary analyses, 52.3% of the TRACE-VCI cohort.

In addition to collecting demographic data (age, sex) and clinical characteristics (vascular risk factors, clinical severity), we gathered information on CSF $A\beta_{1-42}$ levels and pathological status based on validated cut-off values (normal $A\beta_{1-42} \geq 640$ ng/L)[19]. We also collected ApoE genotype and various imaging characteristics, including Fazekas score, medial temporal lobe atrophy score, presence of lacunae, microbleeds, and EPVS. The semiquantitative visual rating of imaging features (Fazekas, MTA, lacunae, microbleeds) was conducted following standard guidelines[3] and previously described methods[18].

Specifically, EPVS were defined on MRI as small, sharply delineated structures with CSF intensity measuring less than 3 mmm and following the course of perforating vessels. EPVS ratings were done using the EPVS rating scale[20] for basal ganglia (BG-EPVS score 0 – 4) and CSO (CSO-EPVS score 0 – 4) based on T2-weigthed images. Ratings were done blinded to clinical information. Intra-rater reliability (IRR) analyses were performed on a subset of the data (n=100), using intraclass correlation for ordinal scales with a two-way random model with absolute agreement. The results demonstrated excellent IRR values for both BG-EPVS (ICC 0.91, 95% CI 0.87 - 0.95) and CSO-EPVS (ICC 0.90, 95% CI 0.83 - 0.94).

Data are presented as frequency (and percentages), median (IQR) or mean (SD). The group was stratified first by Aβ status and then by presence of strictly lobar microbleeds to identify potential confounding variables in demographic, clinical, and imaging characteristics. Comparisons were performed using independent sample t-tests, Mann-Whitney U tests, or Pearson's chi-squared tests, depending on the comparison and data distribution. Post-hoc comparisons of Pearson's chi-squared tests were conducted using pairwise z comparisons, with adjustments for multiple comparisons using the Bonferroni correction.

To analyze the association between Aβ status, the presence of strictly lobar microbleeds, and the likelihood of severe CSO-EPVS burden (defined as >20) [12,21], univariate and multivariate binary logistic regression models were performed. The first multivariate model included an interaction term (Aβ+ status * presence of strictly lobar microbleeds). Additional multivariate models controlled for potential confounders that were identified as significant in the univariate logistic regression analyses. IBM SPSS version 28 was used for all statistical analyses.

Results

The 450 patients had a mean age of 66.5 (± 7.45) years and 45.8% were female. Most patients presented with MCI (n=196, 43.6%) and mild dementia (n= 123, 27.3%). The remaining patients presented with no objective cognitive impairment (n= 93, 20.7%) or moderate dementia (n=35, 7.8%). Among included patients, 57.5% (n=259) exhibited a severe CSO-EPVS burden. Table 1 presents the distribution of severe CSO-EPVS burden in relation to Aβ status and the presence of strictly lobar microbleeds. Severe CSO-EPVS burden was more prevalent in Aβ+ patients (64.8%) compared to Aβ- patients (51.6%), as well as in patients with strictly lobar microbleeds (65.1%) compared to those without (55%). There were no differences in the frequency of severe BG-EPVS burden in Aβ+ patients (13.5%) compared to Aβ- patients (13.1%), as well as in patients with strictly lobar microbleeds (14.4%) compared to those without (11.3%).

Aβ+ patients displayed a higher count of microbleeds (M= 1, η.75= 3, η.90= 50, max 200 vs. Aβ- M= 1, η.75= 1, η.90= 4, max 10) and more frequently displayed strictly lobar microbleeds (Aβ+ 41.7% vs. Aβ- 26.5%, p <.001). Patients with strictly lobar microbleeds were also more frequently Aβ+ (63.2% vs. Aβ- 46.4%, p= .001). In unadjusted univariate logistic analyses, both Aβ+ status (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.18-2.52, p=.005) and the presence of strictly lobar microbleeds (OR 1.53, 95% CI 1.02-2.29, p=.040) were associated with severe CSO-EPVS burden. As shown in Table 2, age was the other only variable significantly associated with a severe CSO-EPVS burden (OR 1.03 per year, 95% CI 1.01-1.06, p=.006). In the multivariate analyses, after adjusting for age, we found that only Aβ+ status (adjusted OR 1.51, 95% CI 1.02-2.24, p=.04) was associated with severe CSO-EPVS, as the presence of strictly lobar microbleeds did not show a significant association (OR 1.39, 95% CI 0.92-2.11, p=.12) with severe CSO-EPVS. We did not observe a significant interaction between Aβ status and the presence of strictly lobar microbleeds regarding the likelihood of severe CSO-EPVS (interaction term Aβ+ status * strictly lobar microbleeds: OR 1.73, 95% CI 0.75-3.96, p=.19).

Discussion

Our results indicate a greater burden CSO-EPVS in patients who exhibit markers of parenchymal and vascular Aβ accumulation. In this setting, markers of CCA were not significantly related to CSO-EPVS burden and we did not observe an interaction between markers parenchymal and vascular Aβ and the likelihood of severe CSO-EPVS.

Our results align with previous studies indicating that CSO-EPVS are a common finding in patients with cognitive impairment [1,9,11,12,22]. The rate of severe CSO-EPVS in our study was similar to that reported in patients with cognitive impairment and CAA[23], but slightly higher compared to other cohorts[4,24]. This discrepancy could potentially be attributed to the higher prevalence of both neurodegeneration and SVD within the TRACE-VCI cohort.

Our findings also demonstrate that while burden of CSO-EPVS was increased in parenchymal and vascular Aβ accumulation, the likelihood of severe CSO-EPVS was

significantly elevated only in Aβ+ patients after adjusting for age as a potential confounding factor. This result partially contradicts a few previously published studies that reported no association between Aβ+ status and severe CSO-EPVS [7–9]. Yet, there are notable methodological differences between these studies and ours, particularly in the type of Aβ biomarker utilized. The use of Aβ CSF biomarkers, as opposed to previous studies utilizing Aβ-PET, may enhance the sensitivity for detecting patients with (early) Aβ accumulation, potentially leading to improved statistical power. The comparison of results using other type of fluid markers, known to be more specific for AD pathology, such as the $A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$ ratio[7,14], which was not available in our cohort, remains uncertain. As the specificity of strictly lobar microbleeds as a surrogate marker for CAA is also not perfect, we tried to overcome potential confounders by excluding participants with mixed cerebral microbleeds.

Prior research investigating the relationship between strictly lobar microbleeds and severe CSO-EPVS in individuals with cognitive impairment has yielded conflicting findings [1,7,12,14]. In our study, we did not identify a distinct association between the presence of strictly lobar microbleeds and severe CSO-EPVS when accounting for age. The disparities between our results and those of other studies should be interpreted considering several discrepancies across the studies, such as differences between the clinical characteristics of the cohorts, how the groups were defined, or how EPVS severity was categorized. These specificities also pose limitations to the generalizability of our findings to other type of clinical or research settings. In terms of cohort characteristics, it is important to note that the TRACE-VCI cohort exhibits a substantial burden of SVD, resulting in a higher prevalence of strictly lobar microbleeds compared to other memory clinic cohorts reported in the literature. While the high prevalence of strictly lobar microbleeds aligns with our objective to examine the association between markers of AD, CAA, and CSO-EPVS, it prompts the question of how the results would manifest in cohorts with different characteristics, such as a lower burden of SVD.

In turn, the frequency of severe BG-EPVS did not differ according to the presence of markers of parenchymal or vascular Aβ deposition. This finding is consistent with views that

argue for different mechanisms underlying EPVS in CSO and BG. EPVS in the basal ganglia are generally thought to be associated with hypertensive microangiopathy, whereas their presence in CSO is most seen in association with CAA [10,12,20,25].

The lack of an interaction between pathological Aβ parenchymal accumulation levels and the presence of strictly lobar microbleeds, which serve as a marker for vascular Aβ accumulation, suggests that both types of Aβ accumulation may not exhibit a synergistic relationship with CSO-EPVS severity in patients presenting with cognitive impairment. However, it is important to consider previous findings from studies focusing on Aβ+ patients with criteria for CAA [10,14] so that we cannot dismiss the possibility that vascular Aβ accumulation might contribute to the association between Aβ parenchymal deposition with CSO-EPVS, potentially reflecting distinct patterns of dysfunction in fluid clearance pathways[5] or different pathological stages [26]. Similar to a recent study on PVS burden and amyloidosis[9], our results do not unequivocally support the hypothesis that CSO-EPVS serves as an exclusive measure of vascular amyloid processes in patients with cognitive impairment.

One limitation of this study is the utilization of standardized semiquantitative visual scores for assessing imaging features, including EPVS ratings. While visual semiquantitative ratings have known limitations in terms of their reliability, they are still considered valid and easy-to-implement methods, especially in cases where automated quantitative approaches are either unavailable or not yet fully validated[27].

Although our study does not specifically address this aspect, it is essential for future research to investigate the association between markers of AD, CAA, and CSO-EPVS burden in patients displaying other imaging markers of CAA or meeting diagnostic criteria for CAA. The significance of this issue is underscored by the inclusion of severe CSO-EPVS as a non-hemorrhagic MRI marker in the Boston criteria v2.0 for CAA [15].

In summary, we provide further evidence that severe CSO-EPVS burden is common in memory clinic patients, particularly in Aβ+ patients. However, the current findings do not

definitively support the notion that severe CSO-EPVS burden serves as a specific indicator of vascular amyloid processes in individuals presenting with cognitive impairment.

Author Contributions

Ana Sofia Costa (Conceptualization; Data Curation; Formal Analysis, Writing - Original draft preparation); Lieza G Exalto (Investigation, Data Curation; Project administration), Wiesje M. van der Flier (Conceptualization; Methodology ; Resources; Funding acquisition), Charlotte E. Teunissen (Conceptualization, Resources), Frederik Barkhof (Conceptualization; Methodology; Resources; Funding acquisition), Hugo J Kuijf (Conceptualization; Methodology; Data Curation), Geert Jan Biessels (Conceptualization; Methodology; Formal Analysis; Writing - Review & Editing; Funding acquisition; Supervision; Project administration).

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Conflict of Interest

The authors report no conflict of interest.

Data Availability

Data of TRACE VCI can be shared upon reasonable request to the corresponding author, while considering data sharing restrictions imposed by the informed consent and privacy and data protection legislation.

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Table 1. Comparison of demographics, clinical and imaging characteristics of TRACE-VCI patients according to Aβ status in CSF and presence of strictly lobar microbleeds

	Aβ status				Strictly lobar microbleeds			
	Aβ-	Aβ+			Absent	Present		
Characteristics	n = 215	n = 235	*P*	ES	n = 295	n = 155	*P*	ES
Age, mean ± SD	64.9 ± 7.6	68.1 ± 7.3	<.001	-0.43	66.2 ± 7.9	67.4 ± 7.1	.13	-0.15
Female sex, n (%)	91 (42.3%)	115 (48.9%)	.19	-0.07	141 (47.8%)	65 (41.9%)	.24	0.06
Diabetes mellitus, n (%)	42 (20%)	31 (13.2%)	.06	-0.09	58 (19.7%)	16 (10.3%)	.011	-0.12
Hypertension, n (%)	174 (80.9%)	192 (81.7%)	.90	-0.02	254 (86.1%)	112 (72.3%)	.001	-0.17
Hypercholesterolemia, n (%)	87 (40.5%)	92 (39.1%)	.85	-0.01	132 (44.7%)	47 (30.3%)	.003	-0.14
Current smoker, n (%)	51 (23.8%)	45 (19.3%)	.25	-0.06	77 (26.3%)	19 (12.3%)	.001	-0.16
Obesity (BMI≥30), n (%)	51 (23.8%)	31 (13.4%)	.010	-0.13	62 (21.2%)	20 (13.2%)	.040	-0.10
History of stroke, n (%)	15 (7.0%)	6 (2.6%)	.040	-0.11	17 (5.8%)	4 (2.6%)	.16	-0.07
Clinical severity			<.001	0.34			.14	0.01
NOCI, n (%)	80 (38.6%)	23 (9.8%)			70 (23.7%)	36 (23.2%)		
MCI, n (%)	52 (24.2%)	53 (22.6%)			76 (25.8%)	29 (18.7%)		
Dementia, n (%)	80 (37.2%)	159 (67.7%)			149 (50.5%)	90 (58.1%)		

Fazekas score, median (IQR)	1 (1-2)	1 (1-2)	.09	0.17	1 (1-2)	1 (1-2)	.002	0.29
MTA score, median (IQR) †	1 (0-1.5)	1 (0.5-2)	<.001	0.47	1 (0-1.5)	1 (0.5-2)	.034	0.20
Presence of lacunae, n (%)	38 (17.7%)	31 (13.2%)	.19	-0.06	48 (16.3%)	21 (13.5%)	.49	-0.04
Presence of strictly lobar microbleeds, n (%)	57 (26.5%)	98 (41.7%)	<.001	0.21	0 (0%)	155 (100%)	-	-
Presence of strictly deep microbleeds, n (%)	14 (6.5%)	13 (5.5%)	.66	0.02	27 (9.2%)	0 (0%)	-	-
EPVS – BG severe burden (>20), n (%)	28 (13.1%)	31 (13.5%)	>.99	0.01	42 (14.4%)	17 (11.3%)	.38	-0.04
EPVS – CSO severe burden (>20), n (%)	110 (51.6%)	149 (64.8%)	.005	0.13	160 (55%)	99 (65.1%)	.040	0.10
$A\beta_{1\text{-}42}$ pathological status (<640 ng/L), n (%)	0 (0%)	235 (100%)	-	-	137 (46.4%)	98 (63.2%)	.001	0.16
ApoE genotype ε4 carrier †			<.001	0.26			.08	0.08
ε4 homozygote carrier	8 (4%)	49 (21.8%)			27 (9.7%)	30 (20.4%)		
ε4 heterozygote carrier	10 (6.1%)	111 (49.3%)			109 (40.3%)	61 (41.5%)		

Abbreviations: BG: Basal ganglia; BMI, body mass index; cSS, cortical superficial siderosis; CSO, centrum semiovale; ES, effect size; IQR, interquartile range; MCI, mild cognitive impairment; ns, not significant; NOCI, no objective cognitive impairment; SD, standard deviation; WMH, white matter hyperintensity.

†N for variables with missing data: MTA score $n_{A\beta-} = 214$; $n_{lmb-} = 294$; ApoE $n_{A\beta-} = 200$ $n_{A\beta+} = 225$. $n_{lmb-} = 278$ $n_{lmb+} = 147$.

Table 2. Results for univariable and adjusted multivariable analyses with severe EPVS-CSO burden as the dependent variable.

Univariate analyses			
Variable	**OR**	**95%CI**	***P***
Age (per year increase)	1.03	1.01-1.06	.006
Aβ+ status	1.72	1.18-2.52	.005
Presence of strictly lobar microbleeds	1.53	1.02-2.29	.040
Presence of diabetes mellitus	0.98	0.59-1.63	.95
Presence of hypertension	1.27	0.79-2.06	.33
Presence of hypercholesteremia	0.94	0.64-1.39	.94
Presence of current smoking	1.22	0.76-1.95	.41
Positive history of stroke	0.69	0.29-1.72	.43
Presence of obesity (BMI ≥30)	0.76	0.46-1.24	.27
Adjusted multivariable model			
Variable	**Adjusted OR**	**95%CI**	***P***
Aβ+ status	1.51	1.02-2.24	.040
Presence of strictly lobar microbleeds	1.39	0.92-2.11	.12

Abbreviations: CI, Confidence interval; OR, Odds ratio
Multivariable model for Aβ+ status and presence of strictly lobar microbleeds adjusted for age