

Association of CSF β -Amyloid Biomarker and Imaging Markers in Cerebral Amyloid Angiopathy

Raffaella Chieffo,^{1,*} Anna Del Poggio,² Marco Vabanesi,¹ Giacomo Giacalone,¹ Miryam Cannizzaro,¹ Beatrice Dell'Acqua,^{1,3} Marco Bacigaluppi,¹ Mario Orrico,¹ Andrea Falini,^{2,3} Nicoletta Anzalone,^{2,3} Massimo Filippi,^{1,3,4,5} and Luisa Roveri^{1,*}

Correspondence

Dr. Chieffo
chieffo.raffaella@hsr.it
or Dr. Roveri
roveri.luisa@hsr.it

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Abstract

Background and Objectives

Cerebral amyloid angiopathy (CAA) is a small vessel disease characterized by β -amyloid deposition in cerebral vessel walls, leading to hemorrhagic and ischemic injuries. The Boston criteria 2.0 guide CAA diagnosis based on clinical and neuroimaging findings. Although imaging-based phenotypes have been well-defined, data on CSF biomarkers remain limited. Integrating CSF and imaging markers may improve understanding of CAA disease patterns. This study evaluates associations between CSF and neuroimaging biomarkers in CAA.

Methods

We retrospectively selected patients with CAA diagnosed according to the Boston criteria 2.0 with available brain MRI and CSF. The amount of cortical superficial siderosis (cSS), the number of cerebral microbleeds (CMBs), enlarged perivascular spaces (EPVSs), and the presence of cortical microinfarcts (CMI) was assessed on brain MRI. Clinical records provided cerebrovascular risk factors and histories of lobar hemorrhage, subarachnoid hemorrhage (SAH), and ischemic stroke. CSF levels of β -amyloid 42 (A β 42), β -amyloid 40 (A β 40), A β 42/40 ratio, total tau, and phosphorylated tau were recorded.

Results

Between June 2021 and May 2024, 23 patients (mean age 72.1 ± 8.4 SD, 52.1% female) met the inclusion criteria. All had lobar CMB and EPVS, while 78.2% had cSS and 65.2% had CMI. Adjusted regression analysis showed that lower A β 40 levels were significantly associated with cSS extent ($B = -0.50$, 95% CI -0.96 to -0.044 ; $p = 0.033$) and CMI count ($B = -0.30$, 95% CI -0.57 to -0.034 ; $p = 0.029$). A lower A β 42/40 ratio correlated with EPVS burden in the centrum semiovale ($B = -0.18$, 95% CI -0.35 to -0.012 ; $p = 0.037$). CMI were significantly associated with SAH ($B = 0.87$, 95% CI 0.23 to 1.51 ; $p = 0.009$). A trend toward an association was observed between EPVS burden and lobar hemorrhage ($B = -0.36$, 95% CI -0.75 to 0.017 ; $p = 0.060$).

Discussion

Lower CSF A β 40 levels were associated with cSS and CMI, while a lower A β 42/40 ratio correlated with EPVS burden. However, the small sample size and the lack of a control group represent a clear limitation, and the results can only have a preliminary and hypothesis-generating value. Further studies are needed to confirm these associations and explore their implications for disease progression and management.

*These authors contributed equally to this work as co-corresponding authors.

¹Neurology Department, IRCCS San Raffaele Scientific Institute, Milan, Italy; ²Department of Neuroradiology and CERMAC, San Raffaele Scientific Institute, Milan, Italy; ³Vita-Salute San Raffaele University, Milan, Italy; ⁴Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; and ⁵Neurophysiology Service, IRCCS San Raffaele Scientific Institute, Milan, Italy.

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Glossary

A β = β -amyloid; **AD** = Alzheimer disease; **CAA** = cerebral amyloid angiopathy; **CMB** = cerebral microbleed; **CMI** = cortical microinfarcts; **cSS** = cortical superficial siderosis; **EPVS** = enlarged perivascular space; **FLAIR** = fluid-attenuated inversion recovery; **IQR** = interquartile range; **minIP** = minimum intensity projection; **p-tau** = phosphorylated tau; **SAH** = subarachnoid hemorrhage; **SWI** = susceptibility-weighted imaging; **t-tau** = total tau.

Introduction

Cerebral amyloid angiopathy (CAA) is a small vessel disease characterized by the deposition of β -amyloid (A β) in the walls of cerebral blood vessels. Clinically, CAA is associated with cognitive impairment, transient focal neurologic episodes, or acute focal neurologic deficits. The most typical disease hallmark of CAA on brain MRI is bleeding, in the form of lobar intracerebral hemorrhage, silent lobar cerebral microbleeds (CMBs), and cortical superficial siderosis (cSS), which is believed to be the chronic manifestation of bleeding from the leptomeningeal vessels.¹ In addition, ischemic brain tissue injuries, such as white matter hyperintensities and microinfarcts, are also prominent features in CAA.² Cerebral cortical microinfarcts (CMI), in particular, have been found to be numerous in autopsy studies and are believed to play a significant role in disease severity.³ Cortical infarcts may remain clinically silent but contribute to the progressive cognitive decline seen in patients with CAA.⁴ Indeed, the ischemic component of CAA may exacerbate neurodegeneration, further complicating the clinical presentation and management of the disease. However, the relationship between CAA, CMB, and cortical infarcts remains poorly understood. Furthermore, enlarged perivascular spaces (EPVSs) are increasingly recognized as a key feature of CAA. Their presence and the degree of enlargement, particularly in the centrum semiovale, correlate with the severity of the disease, making them a potential marker of disease burden.⁵ The variability in CAA neuroradiologic manifestations may stem from distinct pathophysiologic processes and represent different stages of disease progression or individual phenotypic variability.⁶ In this context, CSF biomarkers could provide a valuable means to gain more insights into the different manifestations of CAA.⁷ The existence of a relationship between CSF biomarkers and MRI markers may suggest a role of CSF in helping to broaden the understanding of CAA pathophysiology. Furthermore, the identification of a CSF profile associated with MRI markers of CAA could help to outline disease phenotypes, severity, or stage. To date, the core CSF biomarkers for CAA are the products of amyloid metabolism (A β 40, A β 42, and A β 40/A β 42-ratio), neurodegeneration (total tau [t-tau]), and tangle pathology (phosphorylated tau [p-tau]).⁸ Previous studies have primarily focused on determining whether CSF biomarkers could effectively differentiate CAA from Alzheimer disease (AD) and healthy controls. Some of these studies reported lower levels of A β 42 and A β 40 in CAA compared with controls,^{9,10} while other studies found differences in A β 42^{9,10} or A β 40⁹⁻¹¹ when

comparing CAA with AD. The most recent meta-analysis confirmed that CSF A β 42 and the A β 42/40 ratio can reliably distinguish patients with CAA from controls¹² and that specific CSF patterns of A β 42, A β 40, A β 38, t-tau, and p-tau might serve as molecular biomarkers of CAA.⁸ Less is known about the association of CSF biomarker profiles with CAA neuro-radiologic markers. Previous studies reported lower CSF A β 42^{13,14} and A β 42/40 ratio¹³ levels in patients with cSS or no correlation between A β 42 or A β 40 levels and neuroimaging.¹⁵

The relatively limited data on CSF markers in CAA and the heterogeneity of research to date prompted us to explore the relationship between MRI and CSF biomarkers in patients with probable CAA according to the Boston criteria 2.0,¹⁶ in an attempt to identify possible different disease patterns. Considering the different tendency of A β 40 and A β 42 to deposit mainly in the arterial walls and in the brain parenchyma, respectively,¹⁷ we hypothesize that the neuro-radiologic features of CAA might be reflected in different CSF biomarker profiles.

Methods

Between June 2021 and May 2024, we selected from our database all patients who fulfilled the following inclusion criteria: (1) probable CAA according to the Boston criteria 2.0,¹⁶ (2) availability of a diagnostic cerebral MRI including susceptibility-based sequences (SWI) obtained as standard of care during hospitalization, and (3) availability of the CSF sample obtained as standard of care during hospitalization. Demographic and clinical data extracted from the medical records included age, sex, vascular risk factors (e.g., hypertension, atrial fibrillation, diabetes mellitus, and dyslipidemia), and medications. The occurrence of lobar hemorrhages, subarachnoid hemorrhages (SAHs), and ischemic strokes was assessed by medical history and imaging review.

Brain MRIs were performed at 1.5 tesla field strength, including at least the following sequences: fluid-attenuated inversion recovery (FLAIR), T2-weighted sequences, T1-weighted sequences precontrast and postcontrast, SWI, and with minimum intensity projection (minIP) reconstructions. The SWI sequence was optimized for 1.5T field strengths using high-resolution 3D SWI with thin slices (≤ 2 mm), with a minimized slice gap, and postprocessing with the generation of 10 mm thick minIP slabs to improve continuity

of siderosis and to help visualize microbleeds. Moreover, our standard protocol included the 3D FLAIR sequence which enhances the detection of white matter hyperintensities and SAH, providing better signal uniformity and CSF suppression. We have also used parallel imaging to compensate for longer acquisition times and reduce motion artifacts, using a high-channel head coil (32 channels) to improve the signal-to-noise ratio.

All images were reviewed independently by an expert neuro-radiologist and a vascular neurologist, each with more than 10 years of experience in vascular diseases. Agreement on cases of doubt was reached by consensus. The presence of acute lobar hemorrhage, ischemia, or SAH was first detected. CMB was defined according to the STRIVE-2 criteria,¹⁸ and their presence was categorized in 4 groups (0: none; 1: 1–10; 2: 11–50; and 3: >50) for lobar regions (frontal, parietal, temporal, occipital, and insula) and deep regions (basal ganglia, thalamus, internal and external capsule, corpus callosum, and periventricular white matter). cSS was defined as hypointense curvilinear signal loss on susceptibility-weighted imaging that outlines the outer surface of the cerebral cortex, adjacent subarachnoid space, or both, with no signal CSF alteration in FLAIR sequence. cSS was only rated as present when not associated with acute SAH or contiguous to an intracerebral hemorrhage. The cSS score was assigned according to a previously described rating scale.¹⁹ Each hemisphere was scored separately for cSS as follows: 0: none; 1: 1 sulcus or up to 3 immediately adjacent sulci with cSS; and 2: 2 or more non-adjacent sulci or more than 3 adjacent sulci with cSS. The total cSS score was obtained by summing the 2 hemispheric scores (final range: 0 to 4). According to the STRIVE-2 criteria,¹⁸ we considered CMI as the small cortical infarcts with a size typically ≤ 4 mm. Old CMI were detected on T2-weighted imaging and on FLAIR sequences as hyperintense lesions and on T1-weighted imaging as hypointense lesions. The SWI sequence was used to confirm ischemic cavities and rule out the presence of microbleeds. CMI was quantified in 4 groups (0: none; 1: 1–5; 2: 6–10; and 3: >10). EPVS was detected on T2-weighted sequences and rated as 3-level score (0: none; 1: 1–20; and 2: >20) separately for basal ganglia and centrum semiovale.²⁰

Levels of CSF A β 42, A β 40, A β 42/40 ratio, t-tau protein, and p-tau were measured according to standardized procedures in the local laboratory. The 4 markers were quantified using the Lumipulse G A β 1–42, A β 1–40, t-tau, and p-tau 181 assays by the LUMIPULSE Fujirebio Lumipulse (Tokyo, Japan) automated platform and following the manufacturer's instructions.^{21,22} Laboratory ranges of normality for CSF A β 40 and A β 42 assays were, respectively, 7,755–16,715 ng/L and >599 ng/L; the normality range for the A β 42/40 ratio was >0.069. Tau and p-tau normal values were <404 ng/L and <56.5 ng/L, respectively.

Statistical Analyses

Continuous variables were assessed for normality using the Shapiro-Wilk test and summarized using medians and

interquartile ranges (IQRs) for nonnormally distributed data. First, univariate linear or logistic regression models were constructed to evaluate the relationship between CSF biomarkers (A β 40, A β 42, A β 42/40 ratio, tau, and p-tau) and MRI measurements (lobar CMB, cSS score, cortical infarcts, and EPVS in the centrum semiovale), with CSF biomarkers as independent variables and MRI measurements as dependent variables. Owing to nonnormal distribution, for inclusion in regression models, the levels of CSF biomarkers were log-transformed using the decimal logarithm to normalize their distribution; to facilitate interpretation of regression coefficients, the log-transformed values were multiplied by 10. A multivariate regression model, including relevant CSF biomarkers and demographic data, cerebrovascular risk factors (age, sex, hypertension, dyslipidemia, diabetes mellitus, and atrial fibrillation), and the presence of acute/subacute cerebrovascular events, was developed using backward stepwise selection, retaining in the final model only variables with a *p* value <0.05. Logistic regression models were also built to evaluate the association between hemorrhagic events (lobar and SAH) and MRI measurements. All statistical analyses were performed using SPSS software (IBM SPSS Statistics, version 26), with an alpha level of 0.05 set for determining statistical significance.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted in accordance with the Helsinki Declaration (Fortaleza revision, 2013) and with European and Italian regulations about privacy. Written informed consent was obtained from all participants (or guardians of participants) in the study, as per institutionally approved form. The study does not contain identifying details.

Data Availability

Anonymized data not published within this article will be made available by reasonable request from any qualified investigator.

Results

Twenty-three patients fully respected inclusion criteria and were included in the analysis. Demographic and clinical features are summarized in Table 1. MRI and CSF data were acquired within a median interval of 3 (IQR 1–5) days. Among patients with acute cerebrovascular events (60.8%), 4 had a lobar hemorrhage, 10 had a SAH, and 2 had an ischemic stroke. All participants exhibited CMB and EPVS. cSS was detected in 18 (78.2%) and CMI in 15 (65.2%) patients (Table 1).

Twenty-two patients (95.6%) had both A β 42 and A β 40 CSF levels below laboratory reference lower value, and 21 patients (91.3%) had the CSF A β 42/40 ratio below the laboratory reference cutoff. A β 42 directly correlated with A β 40 levels ($r = 0.7$, $p < 0.0001$). CSF tau levels were above the upper

Table 1 Demographic, Clinical, MRI, and CSF Data

Demographic and clinical data (n = 23)		
Sex, female, n (%)	12 (52.12)	
Age, y, median (IQR)	72 (68–80)	
Hypertension, n (%)	11 (47.8)	
Dyslipidemia, n (%)	11 (47.8)	
Diabetes mellitus, n (%)	3 (13)	
Atrial fibrillation, n (%)	3 (13)	
Antiplatelet therapy, n (%)	8 (34.7)	
Anticoagulant therapy, n (%)	3 (13)	
Antiepileptic therapy, n (%)	9 (39.13)	
Lobar hemorrhage, n (%)	8 (34.7)	
Of which: acute	4 (17.4)	
SAH, n (%)	12 (52.1)	
Of which: acute	10 (43.4)	
IS, n (%)	9 (39.1)	
Of which: acute	2 (8.7)	
MRI measurements (n = 23)		
CMB, n (%)		
0	0 (0)	
1–10	11 (47.8)	
11–49	4 (17.4)	
≥50	8 (34.8)	
cSS score, n (%)		
0	5 (21.7)	
1	3 (13)	
2	5 (21.7)	
3	6 (26.1)	
4	4 (17.4)	
CMI, n (%)		
0	8 (34.8)	
1–5	10 (43.5)	
6–10	4 (17.4)	
>10	1 (4.3)	
EPVS, n (%)	Centrum semiovale	Basal ganglia
0	0 (0)	2 (8.7)
1–20	6 (26.1)	9 (39.1)
>20	17 (73.9)	12 (52.2)
CSF analysis (n = 23)		
Cells, /μL, median (IQR)	2 (1–3.5)	

Continued

Table 1 Demographic, Clinical, MRI, and CSF Data (continued)

Proteins, μL , median (IQR)	44 (35.5–59.5)
A β 40, ng/L, median (IQR)	5,235 (4,810–6,506)
A β 42, ng/L, median (IQR)	234 (212–310)
A β 42/40, ratio, median (IQR)	0.044 (0.041–0.05)
Tau, ng/L, median (IQR)	416 (350–505)
p-tau, ng/L, median (IQR)	62.5 (41.2–73.3)

Abbreviations: A β 40 = amyloid β 1–40; A β 42 = amyloid β 1–42; CMB = cerebral microbleed; CMI = cortical microinfarct; cSS = cortical superficial siderosis; EPVS = enlarged perivascular space; IQR = interquartile range; IS = ischemic stroke; p-tau = phosphorylated tau; SAH = subarachnoid hemorrhage.

laboratory reference value in 11 patients (47.8%), and 12 patients (52.1%) had the CSF p-tau level above the upper laboratory reference value. The univariate regression analysis (Table 2) showed that lower levels of A β 40 were associated with the extent of cSS and the amount of CMI (Figure 1, A and B). Lower A β 42 levels were associated with cSS, and only a trend was observed for the amount of CMI (Figure 1, C and D). At multivariate regression analysis, including A β 40, A β 42, and the cerebrovascular risk factors, only A β 40 levels remained independently associated with the cSS score ($B = -0.50$, 95% CI -0.96 to -0.044 ; $p = 0.033$) and the amount of CMI ($B = -0.30$, 95% CI -0.57 to -0.034 ; $p = 0.029$). The A β 42/40 ratio was significantly and independently associated with the amount of EPVS in the centrum semiovale ($B = -0.18$, 95% CI -0.35 to -0.012 ; $p = 0.037$). The A β 42/40 ratio was lower in participants with a greater number (>20) of EPVS in the centrum semiovale (Figure 2). The CMB score was not associated with any CSF biomarkers (Table 2).

Among the distinctive sign of CAA on MRI, CMI were significantly associated with the occurrence of SAH ($B = 0.87$,

95% CI 0.23 to 1.51; $p = 0.009$). We also found a trend toward an association between the amount of EPVS in the centrum semiovale and the presence of lobar hemorrhage ($B = -0.36$, 95% CI -0.75 to 0.017 ; $p = 0.060$). The CMB score was not associated with any other imaging features of CAA.

Discussion

This retrospective study examined the associations between core CSF and neuroimaging markers in a cohort of patients with probable CAA according to the Boston criteria 2.0 and a standardized brain MRI protocol with SWI sequences in all patients.

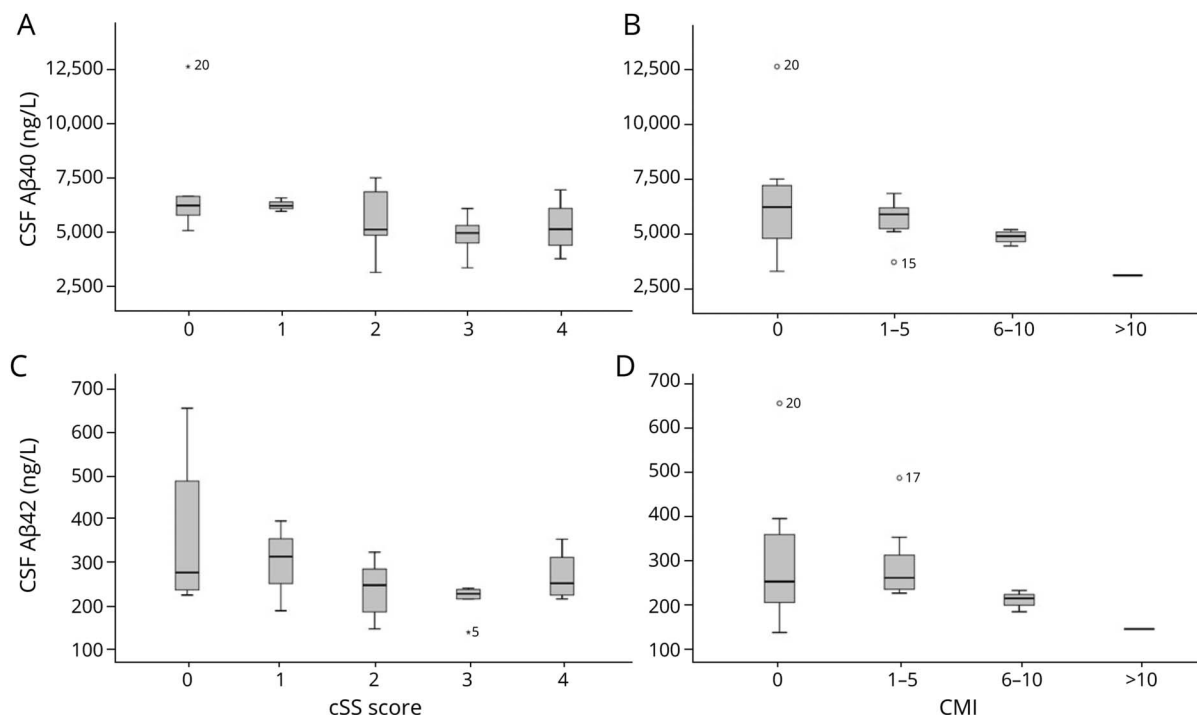
We found that A β 40 was independently associated with cSS. Two previous studies on sporadic CAA reported decreased CSF levels of A β 42 in patients with cSS¹³ and no correlation between A β 42 or A β 40 levels and neuroimaging.¹⁵ The discordant results could probably be attributed to the mixed cohort of patients with possible and probable CAA, as well as the mixed imaging protocols (T2 gradient echo sequences, T2

Table 2 Associations Between CSF Markers and MRI Measurements

	Lobar microbleeds	cSS score	Cortical microinfarcts	Centrum semiovale EPVS
	<i>B</i> (95% CI) <i>p</i> value	<i>B</i> (95% CI) <i>p</i> value	<i>B</i> (95% CI) <i>p</i> value	<i>B</i> (95% CI) <i>p</i> value
A β 40	-0.15 (-0.47 to 0.17) 0.33	-0.5 (-0.96 to -0.044) 0.033*	-0.30 (-0.57 to -0.034) 0.029*	-0.015 (-0.175 to 0.14) 0.85
A β 42	-0.06 (-0.32 to 0.20) 0.67	-0.34 (-0.73 to 0.4) 0.04*	-0.20 (-0.43 to 0.032) 0.087	-0.096 (-0.22 to 0.028) 0.12
A β 42/40	0.09 (-0.30 to 0.48) 0.63	-0.013 (-0.62 to 0.60) 0.96	0.013 (-0.35 to 0.37) 0.94	-0.18 (-0.35 to -0.012) 0.037*
Tau	-0.089 (-0.32 to 0.14) 0.44	-0.29 (-0.64 to 0.056) 0.095	-0.029 (-0.25 to 1.93) 0.78	0.014 (-0.10 to 0.13) 0.81
p-tau	-0.099 (-0.28 to 0.08) 0.28	-0.14 (-0.43 to 0.14) 0.30	-0.049 (-0.22 to 0.12) 0.57	-0.0003 (-0.097 to 0.091) 0.94

Abbreviations: A β 40 = amyloid β 1–40; A β 42 = amyloid β 1–42; cSS = cortical superficial siderosis; EPVS = enlarged perivascular space; p-tau = phosphorylated tau; * = significant value. Results from the univariate linear regression models. All CSF marker levels were log-transformed and multiplied by 10 to facilitate interpretation.

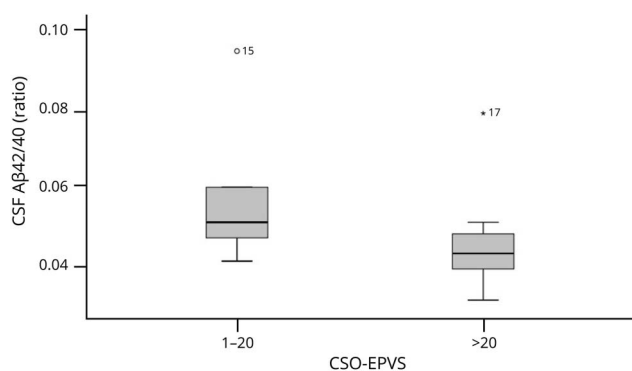
Figure 1 CSF β -Amyloid Measurements, cSS, and CMI



Associations of the cSS score (A-C) and CMI (B-D) with CSF Aβ40 and Aβ42 levels. At multivariate regression analysis, Aβ40 levels were significantly and independently associated with the cSS score ($B = -0.50$, 95% CI -0.96 to -0.044 ; $p = 0.033$) and the amount of CMI ($B = -0.30$, 95% CI -0.57 to -0.034 ; $p = 0.029$). cSS = cortical superficial siderosis; CMI = cortical microinfarcts.

star or a magnetic susceptibility sequence). Another study instead reported the decreasing CSF level of Aβ40 associated with the presence of cSS in patients with Dutch-type CAA.²⁰ A very recent study, including 31 patients with mixed CAA pathology and mixed blood-sensitive MR sequences, reported lower CSF Aβ42 associated with CAA-related ICH, cSS, and severe EPVS in centrum semiovale.¹⁴ However, this study did not measure Aβ40 concentrations, which might be a more

Figure 2 CSF Aβ42/Aβ40 Ratio and EPVS



Association between the amount of centrum semiovale EPVS and Aβ42/Aβ40 ratio. At multivariate regression analysis, the Aβ42/Aβ40 ratio was significantly and independently associated with the amount of EPVS ($B = -0.18$, 95% CI -0.35 to -0.012 ; $p = 0.037$). EPVS = enlarged perivascular space.

accurate measure of severity of vascular amyloid deposition because the authors themselves acknowledge. Furthermore, the most recent meta-analysis on core CSF biomarkers in CAA provided additional evidence of a central role for Aβ40 reductions in accurately differentiating CAA from AD,⁸ reflecting its potential role as a lead biomarker candidate for CAA. Neuropathologic studies indicated that C-terminal configurations of Aβ40 and Aβ42 are present in cerebral vessels.²³ However, although Aβ40 shows a greater tendency to be deposited in the vessel walls of leptomeningeal and cortical arteries,¹⁷ Aβ42 is primarily deposited in CAA-affected capillaries and pericapillary spaces, often in conjunction with parenchymal Aβ42 deposits.^{23,24} Other studies also detected Aβ42 deposits in leptomeningeal vessels, although Aβ40 deposits are more frequent and severe.²⁴ Therefore, it is possible that patients with CAA and predominant cSS may have greater deposition of Aβ40 within the leptomeningeal and cortical vessel walls, and consequently lower level of Aβ40 in the CSF. In addition, we found that reduced CSF Aβ40 levels were associated with CMI. Recently, a histopathologic study on patients with CAA that evaluated amyloid deposition in vessels surrounding CMB and cortical infarcts reported that the density of Aβ-positive cortical vessels was lower around microbleeds and higher around cortical microinfarcts compared with control lesions.²⁵ In addition, single-vessel tracing over serial sections revealed that CMB was associated with extensive vessel wall remodeling. By contrast, cortical infarcts might result from increased Aβ

accumulation and presumed local vessel stiffening. These observations suggest that a single pathophysiologic processes through 2 distinct pathways may lead to hemorrhagic or ischemic lesions.²⁵

Growing neuropathologic and MRI data emphasize the association between cSS, SAH, and CMI,²⁶⁻²⁸ with some studies also reporting spatial overlap.^{27,28} It has been suggested that the ischemic and hemorrhagic expressions of the disease may be related. Cortical spreading depolarizations could be a potential underlying mechanism through which cSS may cause ischemic tissue injury. These depolarizations can occur following acute SAHs and may offer a plausible explanation for transient focal neurologic episodes in affected individuals.²⁹ Alternatively, vascular A β deposition is spatially linked to the loss of vascular smooth muscle cells, which seem to contribute to impaired physiologic reactivity and ischemic brain injury, in the form of cortical infarcts. The loss of normal constituent cells in the vessel wall, although not necessarily a cause of subsequent hemorrhage, seems to be a prerequisite for further remodeling steps, such as fibrin extravasation into the vessel wall.^{25,30} Furthermore, several studies have demonstrated that A β peptides can promote platelet activation, adhesion, and aggregation,^{31,32} potentially inducing ischemic brain injury. Our data indicate that both cSS and CMI are associated with lower CSF A β 40 levels, suggesting greater A β 40 deposition within the leptomeningeal and cortical vessel walls.

It is of interest that we also found an association between the amount of EPVS in the centrum semiovale and the CSF levels of A β 42/40. EPVSs are interstitial fluid-filled cavities around small perforating arteries because they run from the brain surface into the brain parenchyma.³³ These perivascular channels may act as drainage pathways to remove interstitial fluid from the brain, including A β . EPVSs in the centrum semiovale, specifically, has been associated with CAA.^{34,35} Although the mechanisms behind EPVS and their appearance on MRI are not yet fully understood, it seems that the deposition of A β in the walls of cerebral blood vessels, primarily A β 42 in CAA-affected capillaries and pericapillary spaces, impairs the fluid clearance through the perivascular spaces, leading to their enlargement.^{36,37} The CSF A β 42/40 ratio is considered a more accurate marker of amyloid deposition in the brain compared with A β 42 levels alone in AD because the concentration of A β 42 in the CSF depend not only on the physiologic amyloid status but also on the total individual amount of A β peptides.³⁸ Although CSF A β 40 levels are often reduced in CAA, the A β 42/40 ratio is a reliable marker of amyloid pathology, effectively distinguishing patients with CAA from healthy controls,¹² probably given that A β 42 is more prone to aggregation than A β 40. Based on these considerations, our finding of a lower A β 42/40 ratio associated with a greater number of EPVS supports the hypothesis that impaired clearance through enlarged perivascular spaces may further contribute to the accumulation of A β in the brain.^{36,37}

Similarly to previous studies, we found that a greater number of EPVSs in the centrum semiovale were associated with the

occurrence of lobar hemorrhage.^{35,39,40} This finding could suggest that EPVS might be an indicator of an underlying amyloid-related vasculopathy, involving the deposition of A β in parenchymal small vessels that become more susceptible to rupture and hemorrhage. Further studies should explore whether the presence of EPVS may serve as an imaging marker of CAA severity for identifying patients at higher risk for lobar hemorrhage.

The main limitations of this study are the retrospective design, small sample size, and single-center cohort of patients with probable CAA. The retrospective design may have attenuated data quality because we included only patients with available CSF biomarkers and MR imaging. We therefore may have missed patients with CAA and not eligible for CSF or MRI possibly introducing a selection bias. Regarding MRI measurements, despite the high quality of the scans included in our study, the use of a 1.5T strength standard MRI may have underestimated the total burden of CAA markers across the brain in particular regarding CMI. However, unlike previous studies,¹³⁻¹⁵ all patients underwent the same brain MRI protocol with the SWI sequence acquired with the same field strengths reducing the possibility of intersubject variability of measurements. In addition, the lack of a control group is a major limitation of this study, restricting the ability to draw definitive conclusions. In this regard, we would like to point out that the statistical analysis was focused on the relationship between the raw values of CSF and MRI markers of CAA. CSF biomarkers were compared with laboratory reference ranges only for descriptive purposes. The small sample size may have limited our ability to detect some associations. Therefore, our findings should be considered exploratory and hypothesis-generating, rather than hypothesis-confirming. For these reasons, it will be essential to assess the generalizability and replicability of the current results in future studies.

The results should, therefore, be interpreted within the context of the inherent limitations of observational data.

In conclusion, we identified independent associations with the in vivo diagnosis of CAA among imaging and CSF biomarkers. This study may offer insights into the relationships between CSF A β 40 and A β 42 and neuroimaging in patients with CAA. We found that lower CSF A β 40 levels were significantly and independently associated with the extent of cSS and the presence of CMI, emphasizing the role of A β 40 in CAA pathology. In addition, the amount of EPVS in the centrum semiovale was associated with low A β 42/40 ratio. This supports the hypothesis that EPVS might serve as an additional surrogate marker of amyloid accumulation in the brain. Our findings underscore the complex interplay between amyloid pathology, vascular changes, and neuroimaging features in CAA. However, given the small sample size and the lack of a control group, the possibility of drawing conclusions is clearly limited and the results can only have a preliminary and hypothesis-generating value. Further research is necessary to elucidate the mechanisms behind these

associations and their implications for disease progression and management.

Author Contributions

R. Chieffo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A. Del Poggio: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Vabanesi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. G. Giacalone: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Cannizzaro: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B. Dell'Acqua: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Bacigaluppi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Orrico: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Falini: drafting/revision of the manuscript for content, including medical writing for content. N. Anzalone: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Filippi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. L. Roveri: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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