Core cerebrospinal fluid biomarker profile in cerebral amyloid angiopathy

A meta-analysis

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Abstract

Objective

To perform a meta-analysis of 4 core CSF biomarkers (β -amyloid [$A\beta$]42, $A\beta$ 40, total tau [t-tau], and phosphorylated tau [p-tau]) to assess which of these are most altered in sporadic cerebral amyloid angiopathy (CAA).

Methods

We systematically searched PubMed for eligible studies reporting data on CSF biomarkers reflecting amyloid precursor protein metabolism ($A\beta$ 42, $A\beta$ 40), neurodegeneration (t-tau), and tangle pathology (p-tau) in symptomatic sporadic CAA cohorts vs controls and patients with Alzheimer disease (AD). Biomarker performance was assessed in random-effects meta-analysis based on ratio of mean (RoM) biomarker concentrations: (1) in patients with CAA vs healthy controls and (2) in patients with CAA vs patients with AD. RoM >1 indicates higher biomarker concentration in patients with CAA vs comparison population and RoM <1 indicates higher concentration in comparison groups.

Results

Three studies met inclusion criteria. These comprised 5 CAA patient cohorts ($n = 59$ patients) vs healthy controls ($n = 94$ cases) and AD cohorts ($n = 158$). Three core biomarkers differentiated CAA from controls: CSF $A\beta$ 42 (RoM 0.49, 95% confidence interval [CI] 0.38–0.64, $p < 0.003$), $A\beta$ 40 (RoM 0.70, 95% CI 0.63–0.78, $p < 0.0001$), and t-tau (RoM 1.54, 95% CI 1.15–2.07, $p = 0.004$); p-tau was marginal (RoM 1.24, 95% CI 0.99–1.54, $p = 0.062$). Differentiation between CAA and AD was strong for CSF $A\beta$ 40 (RoM 0.76, 95% CI 0.69–0.83, $p < 0.0001$), but not $A\beta$ 42 (RoM 1.00; 95% CI 0.81–1.23, $p = 0.970$). For t-tau and p-tau, average CSF ratios in patients with CAA vs patients with AD were 0.63 (95% CI 0.54–0.74, $p < 0.0001$) and 0.60 (95% CI 0.50–0.71, $p < 0.0001$), respectively.

Conclusion

Specific CSF patterns of $A\beta$ 42, $A\beta$ 40, t-tau, and p-tau might serve as molecular biomarkers of CAA, but analyses in larger CAA cohorts are needed.

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Glossary

A β = β -amyloid; AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; CI = confidence interval; ICH = intracerebral hemorrhage; p-tau = phosphorylated tau; RoM = ratio of means; t-tau = total tau.

Sporadic cerebral amyloid angiopathy (CAA) is a common degenerative small vessel disease of the brain, associated with spontaneous lobar intracerebral hemorrhage (ICH) and vascular cognitive impairment in the elderly.^{1,2} The neuropathologic hallmark of CAA is progressive deposition of β -amyloid (A β) within the walls of cortical and leptomeningeal small arterioles. In contrast to the parenchymal amyloid depositions found in Alzheimer disease (AD), which mostly consist of the 42-amino acid form (A β 42), CAA contains both A β 40 and A β 42, with A β 40 being the major isoform. The diagnosis of CAA currently relies on the detection of characteristic multiple strictly lobar hemorrhagic lesions on neuroimaging (ICH, cerebral microbleeds, and cortical superficial siderosis), using the Boston criteria in the appropriate clinical context.^{3,4}

Emerging data suggest that CAA is associated with a range of hemorrhagic ischemic markers on structural neuroimaging, as well as markers of vascular physiology alterations.⁵ However, potential CAA biomarkers outside the Boston criteria do not generally have strong support, or adequate validation. Even the use of key MRI signatures of CAA remains limited in reflecting the pathologic consequences of rather advanced disease.⁶ The various CAA-related MRI structural lesions essentially represent vascular-mediated brain damage, rather than abnormalities of CAA-laden vessels themselves.⁵ They hence seem to provide only indirect evidence of late and irreversible CAA consequences. Identifying CAA at an early stage, i.e., before the appearance of multiple hemorrhagic lesions, or in patients without predominantly hemorrhagic CAA presentations remains extremely limited, but can provide valuable insights in the design of preventive trials.

CSF molecular biomarkers offer another approach that might prove useful in more directly measuring underlying CAA aspects, in particular A β levels. While decreased levels of CSF A β 42, but not A β 40, are found in AD,⁷ small preliminary studies suggest that both A β 42 and A β 40 concentrations are decreased in CAA relative to healthy controls and patients with AD, without associated increased tau levels.⁸ However, no meta-analysis has been performed on the topic, partly because traditional approaches (i.e., standard mean difference of biomarkers concentration) are challenging in light of the large variability between laboratories and assays measuring CSF biomarkers.

Using a novel approach of generating fold change of mean biomarker concentration (i.e., ratio of the means),⁹ we performed a systematic review and meta-analysis to examine and synthesize current data on the CSF profile of patients with symptomatic CAA (vs healthy elderly controls and patients

with AD) in 4 core biomarkers of brain amyloid load and neurodegenerative processes: A β 42, A β 40, total tau (t-tau), and phosphorylated tau (p-tau).

Methods

We conducted this study with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,¹⁰ Meta-analysis of Observational Studies in Epidemiology guidelines,¹¹ and according to a prespecified protocol developed in-house.

Search strategy and selection criteria

We searched PubMed until May 21, 2017, using a combination of keyword search and MeSH terms: (CSF or “cerebrospinal fluid”) and (“cerebral amyloid angiopathy” or CAA or “amyloid angiopathy”). Reference lists from all included articles, review articles on the topic, and the authors’ own files were also searched for relevant studies. A similar search was performed in Web of Science, but no unique studies in addition to the PubMed search results were identified. We included studies (without language restriction) that reported data on CSF biomarkers of amyloid metabolism (A β 42, A β 40), neurodegeneration (t-tau), and tangle pathology (p-tau) in patients with symptomatic sporadic CAA (main group) vs relevant controls (healthy elderly or patients without brain amyloid diseases) or vs patients with AD. Sporadic CAA was defined according to the original or modified Boston criteria^{3,12,13} in patients who presented with either symptomatic lobar ICH or transient focal neurologic episodes related to isolated cortical superficial siderosis or convexity subarachnoid hemorrhage. The control group consisted of patients without neurologic disorders primary related to brain amyloid deposition or healthy controls.

Articles were excluded if instead of sporadic CAA they included hereditary CAA, CAA-related inflammation cases, or only asymptomatic “suspected” CAA cases based on the presence of silent strictly lobar cerebral microbleeds (for example, studies comparing AD or memory clinic patients with vs without strictly lobar microbleeds). Studies were also excluded if they did not contain a control group or a comparison AD cohort, or had CAA cohorts with fewer than 10 patients in total or fewer than 5 patients in different CAA presentation subgroups (these cutoffs were arbitrary, to exclude case reports or small case series of 2–3 patients). For cohorts with more than one publication from overlapping cases, we included the publication with the higher number of cases. Three authors independently screened potentially eligible publications for inclusion and the final list was decided upon consensus.

Data extraction

Two authors (A.C. and A.V.) extracted data from all eligible studies on comparison groups, CAA clinical presentation, CSF analysis methods, and basic design aspects where relevant. For all groups, the CSF levels of the 4 core biomarkers were extracted (or estimated as suggested by Wan et al.¹⁴) as mean concentrations with SD.

Risk of bias assessment

The methodologic quality of each selected study was assessed using the revised Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2)¹⁵ tool,^{16,17} with additional items from the Standards for Reporting Diagnostic Accuracy (STARD) 2015.¹⁸ We have also included an additional criterion describing the overall evidence assessment of each study. Nonconsecutive and nonprospective studies were classified as medium quality.

Theoretical framework and statistical synthesis

The variability in CSF biomarker concentrations between laboratories and assays and potential different cutpoints to differentiate patient groups makes a traditional meta-analysis of standard mean differences challenging. To reduce these problems, we have adopted the approach of generating fold change, by using the ratio of means (RoM) as the effect measure, calculated as CSF biomarker concentration between groups of interest. This method controls for the variability in concentration ranges between studies. We meta-analyzed patients with CAA to healthy control groups and patients with AD ratios of CSF biomarker concentrations (A β 42, A β 40, t-tau, and p-tau). Each ratio was generated within each individual study for every comparison of interest. A ratio above 1 indicates that the concentration of the biomarker is higher in the CAA patient population vs comparison population, and a ratio below 1 indicates the concentration is higher in the comparison groups.

In studies with more than one CAA patient group based on clinical presentation, separate CSF biomarker ratios per CAA subgroups compared to healthy controls and patients with AD were generated. The rationale for this approach is that inclusion methods, patient characteristics, and CSF marker relevance are different depending on CAA cohort clinical phenotype.

Standard errors of the RoM CSF values were calculated using the delta method, as previously described,^{19–21} and mean values are presented with 95% confidence intervals (CIs). A *p* value of 0.05 or less was considered significant. Random effects meta-analysis using the method of DerSimonian and Laird²² with the estimate of heterogeneity taken from the inverse variance model was performed in Stata (version 13). Random effects models were chosen because these incorporate between-study heterogeneity and give wider (i.e., more conservative) CIs when heterogeneity is suspected.

Results

Three studies were included in the final systematic review and meta-analysis (figure 1 for flowchart), reporting data useful to address the concentration ratios of CSF biomarkers in patients with CAA vs controls and vs patients with AD.^{8,23,24} One study included a single group of patients with CAA presenting with lobar intracerebral hemorrhage.⁸ Two studies included 2 CAA patient cohorts each.^{23,24} One of these studies had a CAA patient group presenting with lobar intracerebral hemorrhage and a CAA cohort without lobar intracerebral hemorrhage presenting with cortical superficial siderosis and transient focal neurologic episodes.²³ The other study had a CAA cohort presenting with acute convexity subarachnoid haemorrhage and transient focal neurologic episodes and a second CAA patient group without acute convexity subarachnoid haemorrhage identified from a memory clinic.²⁴ The funnel plots suggested no publication bias for all 4 core biomarkers (results not shown).

Table 1 summarizes key characteristics of included groups and relevant methodologic aspects across studies. Table 2 shows the results of the quality assessment; in general, included studies were of medium quality. A total of 5 CAA cohorts (*n* = 59 patients) vs appropriate control groups (*n* = 94 cases) and AD groups (*n* = 158) were pooled in meta-analyses.

We first meta-analyzed data on the 4 core CSF biomarkers (A β 42, A β 40, t-tau, and p-tau) in CAA patient vs control groups. The CSF A β 42 RoM and A β 40 RoM between CAA patients to controls were both below 1, with a pooled value of 0.49 (95% CI 0.38–0.64, *p* < 0.001) and 0.70 (95% CI: 0.63–0.78, *p* < 0.0001), respectively (figure 2, A and B). For t-tau, the CAA patients to controls CSF RoMs were above 1, with a pooled value of 1.54 (95% CI 1.15–2.07, *p* = 0.004) (figure 2C). In the case of p-tau, the CAA patient to controls analysis resulted in a pooled RoM of 1.24 (95% CI 0.99–1.54), which did not reach statistical significance (*p* = 0.062) (figure 2D).

Second, we meta-analyzed reported data for the same 4 core CSF markers in patients with CAA vs patients with AD. The CSF concentration of A β 42 did not differ between the 2 groups (pooled RoM 1.00; 95% CI 0.81–1.23, *p* = 0.970; figure 3A). By contrast, the CSF A β 40 RoM between patients with CAA and patients with AD was below 1 in all cohort comparisons, and had a pooled RoM of 0.76 (95% CI 0.69–0.83, *p* < 0.0001; figure 3B). For t-tau and p-tau, CSF RoMs were below 1 in patients with CAA vs patients with AD (figure 3, C and D), with pooled values of 0.63 (95% CI 0.54–0.74, *p* < 0.0001) and 0.60 (95% CI 0.50–0.71, *p* < 0.0001), respectively.

In a post hoc sensitivity analysis, excluding the CAA patient group presenting without acute convexity subarachnoid hemorrhage from one study²⁴ (table 1) (since only half of the

Figure 1 Flow chart of study selection

patients presented with acute symptoms) did not change any of our results or effect sizes (data not shown).

Discussion

In this systematic review and meta-analysis, we brought together available evidence on whether a specific pattern of A β and tau protein concentrations in CSF of patients with symptomatic CAA exists. Our results suggest that CAA (largely without dementia) is characterized by a CSF pattern, distinct from either healthy controls or patients with AD, of decreased A β 40 levels with marginally elevated tau protein, especially t-tau. A β 42 in the CSF of patients with CAA was lower than in controls but similar to patients with AD (consistent with A β 42 but not A β 40 being predominantly present in amyloid depositions of patients with AD), and CSF tau proteins in CAA, though higher than controls, was lower than in AD. An important finding to note is the limited number of studies on the topic from which these results are derived—based on 5 CAA cohorts, including around 60 patients in total. Hence, our finding should be considered preliminary and hypothesis-generating. However, the reported overall effect sizes of CSF marker performance (i.e., fold change) provide actionable data useful for future studies in a growing biomarker CAA landscape.⁵ This includes reporting the range of changes in the core CSF biomarkers, i.e., 30%–50% lower A β

levels and 24%–54% higher tau protein levels in patients with CAA vs controls, and 24% lower A β 40 (but similar A β 42) and 37%–40% lower tau protein levels in CAA vs AD. These estimates can be directly compared with the effect sizes of other biomarkers in the field, different CAA presentations, and in longitudinal studies.

Three core CSF biomarkers of neurodegeneration have been consistently and strongly associated with AD and are now used in routine clinical practice and research.⁹ These include A β 42, found at low concentrations in patients with AD (vs controls) due to cortical parenchymal amyloid deposition, t-tau at high concentrations related to cortical neuronal loss, and high concentrations of p-tau, reflecting cortical tangle formation.⁹ As reported in an early study in the field, our results are striking given the known overlap between CAA and AD at the neuropathologic level.⁸ The majority of patients diagnosed with AD have some degree of cerebrovascular amyloid deposition (usually mild), and those diagnosed with symptomatic CAA have different burden of cerebrovascular amyloid deposition and often have incipient amyloid plaque pathology, but not to the extent that a diagnosis of dementia is considered relevant.¹ Despite this overlap, our results suggest that the predominance of one pathology relative to the other is strong enough to generate distinct CSF patterns in the appropriate clinical context.

Table 1 Characteristics of included studies and different comparison groups

Study	CAA groups, n, age, per presentation	Control cases type, n, age	AD group, n, age	CSF analysis	Notes on analyses/ results
Renard et al.²³	A. CAA-LICH: n = 18, 73 y; 5 probable, 13 possible CAA; no preexisting cognitive impairment (as reported by patients/family)	Patients without amyloid-related brain disease ^a (all >60 y old)	NIA core clinic and imaging diagnosis criteria (blinded to CSF)	CSF analysis blinded to diagnostic group	T2 ^a MRI available in CAA groups for diagnostic classification based on CMB and cSS
	B. CAA non-LICH (modified Boston criteria): patients with isolated cSS presenting with TFNE; n = 10, 78.5 y	No cognitive impairment	Probable AD per NINCDS-ADRDA	ELISA kits (Innotest β-amyloid 1-42, IBL β-amyloid 1-40, h-tau, and phospho-tau [¹⁸¹ P], Innogenetics, Ghent, Belgium)	Control group and AD without CMB/cSS on brain MRI
	No preexisting CI (as reported by patients/family)	Retrospectively selected from a single-center registered CSF certified biobank	Mean MMSE: 19 (SD 5.5); n = 42, 73 y (all >60 y old)		No differences between possible vs probable CAA-LICH and CAA non-LICH patients with and without FLAIR hyperintense (i.e., acute) cSS
	MMSE >27 in 9 cases at baseline		Retrospectively selected, with methods similar to controls		Diagnostic accuracy estimates provided in a previous publication of overlapping series ³⁴
	No cognitive impairment after 10 mo mean follow-up (range 2–17)				
Martínez-Lizana et al.²⁴	A. CAA without acute cSAH: cognitive impairment (n = 6), TFNE (n = 6); n = 12, mean age 69.8 y (range 52.1–83.7) (probable CAA per modified Boston criteria)		Per NINCDS-ADRDA criteria; n = 44, mean age 67.6 y (range 50.6–79.8)	ELISA kits: Aβ42 (Innotest β-amyloid 1-42, Innogenetics), Aβ40 (Millipore), t-tau (Innotest hTAU Ag, Innogenetics) and p-tau 181p (Innotest phospho-tau 181p, Innogenetics)	Convenience sample, multicenter cohort, not consecutive patients
	All patients were assessed in a memory clinic		Drawn similar to controls		
	B. CAA with acute cSAH: with acute cSAH and TFNE, all >60 y old	Healthy controls			
	Previous ICH in 2 patients, n = 7, mean age ~79 y; some with cognitive impairment at baseline or follow-up (CDR-SOB 0.5–12)	No cognitive impairment after neuropsychological evaluation n = 20, mean age 66.5 y (range 55.7–77.5)			
Verbeek et al.⁵	CAA-LICH: n = 17, mean age ± SD 62.8 ± 11.9 y (probable or definite CAA per original Boston criteria)	Healthy controls n = 58, mean age ± SD 61.0 ± 8.7 y (all >50 y)	Probable AD per NINCDS-ADRDA; n = 72, mean age ± SD 69.4 ± 8.3 y	ELISA (Innogenetics NV, Gent, Belgium)	MRI not performed in AD group
	11 without CI, 6 with MCI, none with dementia	Patients visited the RUNMC outpatient clinic (various reasons) but turned out to have no neurologic disorder	Derived from RUNMC patient database with cognitive impairment or dementia of various origins (1992–2007)		ROC analysis for optimal differentiation of CAA from controls presented

Abbreviations: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; CDR = Clinical Dementia Rating; CMB = cerebral microbleeds; cSAH = convexity subarachnoid hemorrhage; cSS = cortical superficial siderosis; FLAIR = fluid-attenuated inversion recovery; LICH = lobar intracerebral hemorrhage; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (Alzheimer disease criteria); p-tau = phosphorylated tau; ROC = receiver operating characteristic; RUNMC = Radboud University Nijmegen Medical Center; SOB = sum of boxes; t-tau = total tau; TFNE = transient focal neurologic episodes. Age is reported as mean age for Martínez-Lizana et al. and as number of years for Renard et al.

^a Final diagnoses of the control group: depression (n = 7), normal pressure hydrocephalus (n = 4), peripheral nerve disorder (n = 2), meningioma (n = 1), cervical myelopathy due to arthropathy (n = 1), and ischemic brain infarction (n = 1).

Table 2 Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2) assessment of risk of bias for included studies, individually

Study	Risk of bias (QUADAS-2)				Applicability concerns (QUADAS-2)			Extra criteria (from STARD 2015)			
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	Readers of index test described	Diagnostic accuracy estimates	Blinding	Overall evidence
Renard et al. ²³	↓	↓	↓	↓	↑	↓	↓	No	No	Yes	Medium
Martínez-Lizana et al. ²⁴	↑	↓	?	↑	↑	↓	?	No	No	No	Medium
Verbeek et al. ⁸	↓	↓	↓	↑	↓	↓	↓	No	Yes	No	High

Abbreviation: STARD = Standards for Reporting Diagnostic Accuracy.
 ↓ = Low risk; ↑ = high risk; ? = unclear risk.

We confirmed that this CSF profile in patients with symptomatic CAA seems to entail the presence of both low Aβ42 and Aβ40 levels when compared to controls, with Aβ42 levels close to what is seen in patients with AD, but lower

Aβ40 levels. The t-tau in CAA shows intermediate levels between controls and patients with AD (i.e., higher than controls, but lower than AD), in line with recent data demonstrating increased cortical atrophy in patients with

Figure 2 Cerebral amyloid angiopathy (CAA) to control group (healthy controls or control group without amyloid-related brain disease) ratio for CSF Aβ42, Aβ40, total tau (t-tau), and phosphorylated tau (p-tau)

Ratio for CSF Aβ42 (A), Aβ40 (B), t-tau (C), and p-tau (D). Outcome measures are given as the overall ratio between CAA patients and comparison groups. Individual study ratios and their corresponding 95% confidence intervals (CIs) are indicated by filled squares. The size of the square indicates the weight of the study. The overall pooled ratio and 95% CI is indicated by a diamond. The solid line indicates a ratio of 1 and the dotted line indicates the average ratio. RoM = ratio of means.

Figure 3 Cerebral amyloid angiopathy (CAA) to Alzheimer disease ratio for CSF A β 42, A β 40, total tau (t-tau), and phosphorylated tau (p-tau)

CAA to Alzheimer disease ratio for CSF A β 42 (A), A β 40 (B), total tau (t-tau) (C), and phosphorylated tau (p-tau) (D). Outcome measures are given as the overall ratio between patients with CAA and comparison groups. Individual study ratios and their corresponding 95% confidence intervals (CIs) are indicated by filled squares. The size of the square indicates the weight of the study. The overall pooled ratio and 95% CI is indicated by a diamond. The solid line indicates a ratio of 1 and the dotted line indicates the average ratio. RoM = ratio of means.

CAA compared to healthy elderly controls.²⁵ P-tau levels in patients with CAA are, in general, 24% higher than seen in controls (but the increase did not quite achieve statistical significance at the $p = 0.05$ level), and significantly lower than in patients with AD. Similar patterns have been recently demonstrated in both symptomatic and pre-symptomatic mutation carriers with hereditary cerebral hemorrhage with amyloidosis–Dutch type, a model for sporadic CAA in which patients are younger and have a pure form of cerebrovascular amyloid deposition without the confounding effect of concomitant AD changes.²⁶ In addition, higher lobar microbleed counts, white matter hyperintensities volume, and cortical superficial siderosis (all putative CAA MRI markers) were correlated with decreasing A β 40 concentration.²⁶ These CSF profile findings are broadly consistent with the pathologic hallmarks of CAA, which include vascular deposition of A β 40 (predominantly) and to a lesser extent A β 42, but inconsistent coexistence of tau-containing lesions, especially in patients with symptomatic CAA presenting with hemorrhage.²⁷

Due to the small number of studies, our meta-analysis is not powered to investigate potential differences in these CSF profile across the CAA symptomatic presentations spectrum. Judging from largely overlapping 95% CI in our forest plots, striking differences are unlikely. This is in line with data demonstrating that cerebrovascular amyloid burden is similar (and already advanced) in both CAA-ICH and CAA without ICH clinical presentations.²⁷

Another important aspect is the role of differences of mean age across groups and studies in our analysis (table 1), which might have implications for CSF levels. Increasing age is among the strongest risk factors for CAA,²⁸ and a risk factor for AD-related neurodegeneration.²⁹ It is thus conceivable that higher mean age of CAA groups might result in even more striking CSF A β 40 level differences vs comparison groups, but less differences in the levels of the rest of the markers due to higher likelihood of concomitant AD pathology. However, most of the patients included in the main CAA groups had sentinel symptomatic presentations of the disease (a key focus of our

article) and it is hence plausible that they already harbor advanced vascular amyloid pathology, independent of age.²⁸ Future studies should ideally include age-matched comparison groups (healthy controls, AD) and also consider including younger healthy groups (i.e., <55 years of age) to derive diagnostic cutoffs.^{30–32}

The main limitation of our study is the small sample size, which reflects the limited number of available CSF data in the field. Furthermore, studies reviewed here were not prospective; patients with CAA had different characteristics, disease duration, and disease severity. This is a well-appreciated bias source in diagnostic test accuracy studies and might explain the moderate statistical heterogeneity identified in some of our analyses. Despite the limited data, and the potential selection bias, we could still demonstrate significant differences and a specific profile of CSF biomarkers in CAA. It is important to note that some of the patients with symptomatic CAA examined had cognitive impairment, despite this not being the predominant clinical presentation. This suggestion of possible concomitant AD or other types of dementia potentially influence the CSF biomarker results and contribute to increased heterogeneity. Finally, the control and AD patient groups did not routinely have MRI as part of the study. Hence, the presence of preclinical or incipient CAA pathology, often found in a substantial proportion of elderly individuals and patients with AD,¹ could not be ruled out. However, any undetected CAA in the control and AD groups would be expected to bias against significant differences in CSF profiles, making the observed differences even more striking. Further meta-analyses should assess CSF profiles in relation to MRI biomarkers of cerebral small vessel disease, including cerebral microbleeds in other clinical settings (i.e., unselected memory clinic populations, AD) and in healthy elderly. This approach might be useful in gaining pathophysiologic insights into different small vessel disease MRI profiles. Of note, this was beyond the scope of our initial meta-analysis protocol, since we aimed to investigate CSF biomarker profiles in relatively “pure” symptomatic presentations, which can more clearly be attributed to sporadic CAA.⁵ This initial approach might be useful in providing actionable effect size data for the design of larger clinical CSF diagnostic accuracy studies in the CAA field.⁵

Our analysis is hypothesis-generating and provides preliminary effect size estimates based on the totality of current evidence about CSF profile in patients with sporadic CAA. Together with recent data on amyloid PET, these results suggest that molecular biomarkers might be useful to identify cerebrovascular A β .^{5,33} Further larger prospective studies are needed to externally validate these results, formally test the diagnostic accuracy of the core CSF markers (A β 42, A β 40, t-tau, and p-tau), as an add-on to the clinical diagnostic pathway, especially in clinical situations where CAA diagnosis based on MRI findings alone is not clear. Such clinical scenarios might include suspected CAA cases, which do not fulfill Boston criteria for probable CAA (the category with the highest diagnostic accuracy): patients with an

isolated lobar ICH without microbleeds (i.e., possible CAA), single or a few lobar microbleeds only, and patients with isolated cortical superficial siderosis. Future studies should also determine whether CSF markers could be useful as a quantitative measure of CAA severity and progression, potentially predicting the effects of CAA on cerebrovascular dysfunction and small vessel brain injury.⁵

Author contributions

A. Charidimou: study concept and design, systematic review, data collection, analysis, writeup. J. O. Friedrich: analysis advice, critical revisions. Steven M. Greenberg: critical revisions. Anand Viswanathan: critical revisions.

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Core cerebrospinal fluid biomarker profile in cerebral amyloid angiopathy

A meta-analysis

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Study question

Can amyloid- β 40 (A β 40), amyloid- β 42 (A β 42), total tau (t-tau), and phosphorylated tau (p-tau) serve as CSF biomarkers for sporadic cerebral amyloid angiopathy (CAA)?

Summary answer

A β 40, A β 42, t-tau, and p-tau may serve as potential CSF biomarkers for CAA after further validation.

What is known and what this article adds

The standard diagnostic criteria for CAA currently consist of neuroimaging findings, but CSF biomarkers may provide more direct evidence for CAA. This meta-analysis provides evidence for the utility of CSF biomarkers and their effect sizes in distinguishing patients with CAA from healthy controls and patients with Alzheimer disease (AD).

Participants and setting

The 3 studies examined in this meta-analysis collectively included 59 patients with CAA, 94 healthy controls, and 158 patients with AD.

Design, size, and duration

This meta-analytic study used a PubMed search to find studies that examined CSF A β 40, A β 42, t-tau, and p-tau levels in patients with CAA, healthy controls, and patients with AD.

Primary outcomes

The primary outcomes for the 4 CSF biomarkers were fold changes, determined through ratio of mean (RoM) calculations, in biomarker concentration between the CAA and healthy control groups and between the CAA and AD groups.

Main results and the role of chance

The CAA and healthy control groups could be distinguished with A β 42 (RoM, 0.49; 95% CI, 0.38–0.64; $p < 0.003$), A β 40 (RoM, 0.70; 95% CI, 0.63–0.78; $p < 0.0001$), and t-tau (RoM, 1.54; 95% CI, 1.15–2.07; $p = 0.004$) but not with p-tau (RoM, 1.24; 95% CI, 0.99–1.54; $p = 0.062$). The CAA and AD groups could be distinguished with A β 40 (RoM, 0.76; 95%

CI, 0.69–0.83; $p < 0.0001$), t-tau (RoM, 0.63; 95% CI, 0.54–0.74; $p < 0.0001$), and p-tau (RoM, 0.60; 95% CI, 0.50–0.71; $p < 0.0001$) but not with A β 42 (RoM, 1.00; 95% CI, 0.81–1.23; $p = 0.970$).

Bias, confounding, and other reasons for caution

This meta-analysis was limited by small sample sizes. Furthermore, the reviewed studies were not prospective. Some of the patients with CAA might have had concomitant AD, and some of the healthy controls and patients with AD might have had incipient CAA.

Generalizability to other populations

The patients with CAA had heterogeneous clinical characteristics, which makes the generalizability to patients with specific characteristics unclear.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.