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ORIGINAL RESEARCH

Cerebrospinal Fluid β-Amyloid and τ Levels in Patients With Iatrogenic Cerebral Amyloid Angiopathy, Sporadic Cerebral Amyloid Angiopathy, Alzheimer Disease, and Controls

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BACKGROUND: Iatrogenic cerebral amyloid angiopathy (iCAA) is a subform of cerebral amyloid angiopathy caused by exposure to amyloid β. The aim of this study was to assess cerebrospinal fluid amyloid and τ concentrations in iCAA in comparison with sporadic cerebral amyloid angiopathy (sCAA), Alzheimer disease (AD), and controls.

METHODS: We conducted a systematic literature review to identify patients with iCAA with published cerebrospinal fluid marker concentrations. We then analyzed the cerebrospinal fluid concentrations of amyloid β40, amyloid β42, total τ, and phosphorylated τ 181, comparing them with the corresponding data of patients with sCAA, AD, and controls from our previous work.

RESULTS: The study included 25 patients with iCAA (age, 44±11 years), 31 patients with sCAA (age, 75±5 years), 28 patients with AD (age, 71±8 years) and 30 controls (age, 72±8 years) from 9 case descriptions and 1 cohort study. Amyloid β40 concentrations did not differ significantly between iCAA and the other groups. Amyloid β42 concentration was significantly higher in controls than iCAA and the other groups. The amyloid β42/40 ratio was higher in iCAA than in AD and higher in controls than sCAA and AD. Total τ concentrations were lower in controls than iCAA but did not differ significantly between iCAA, sCAA, and AD. Phosphorylated τ concentrations were not significantly different in iCAA compared with controls, significantly higher in sCAA, and highest in AD.

CONCLUSIONS: The observation that phosphorylated τ concentrations in iCAA are not different from controls led us to the hypothesis that iCAA is characterized by amyloid plaque formation largely without concomitant phosphorylated τ aggregation, which is well compatible with most published pathologic studies.

Key Words: phosphorylated τ ■ Alzheimer disease ■ amyloid β ■ amyloid β40 ■ amyloid β42 ■ CSF ■ iatrogenic cerebral amyloid angiopathy ■ τ ■ total τ

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CLINICAL PERSPECTIVE

What Is New?

- Biomarkers are not yet included in the diagnostic criteria for iatrogenic cerebral amyloid angiopathy.
- The amyloid β42/40 ratio is higher in iatrogenic cerebral amyloid angiopathy than in Alzheimer disease and phosphorylated τ concentrations in patients with iatrogenic cerebral amyloid angiopathy are not different from controls while being higher in sporadic cerebral amyloid angiopathy and Alzheimer disease.

What Are the Clinical Implications?

- Cerebrospinal fluid biomarkers could be used to diagnose iatrogenic cerebral amyloid angiopathy and differentiate it from sporadic cerebral amyloid angiopathy and Alzheimer disease.

Nonstandard Abbreviations and Acronyms

CAA	cerebral amyloid angiopathy
iCAA	iatrogenic cerebral amyloid angiopathy
sCAA	sporadic cerebral amyloid angiopathy

Iatrogenic cerebral amyloid angiopathy iCAA) is a subform of cerebral amyloid angiopathy (CAA) caused by a remote exposure to materials contaminated with amyloid β. The symptoms start decades after the exposure, which usually occurred during a neurosurgical operation conducted before the 1990s. The clinical presentation is similar to sporadic CAA (sCAA; intracerebral and subarachnoid hemorrhage, transient focal neurological episodes, seizures, and cognitive decline) but at a younger age.[1]

It has been hypothesized that a vascular accumulation of amyloid β occurs in iCAA, resulting in decreased values of amyloid β in the cerebrospinal fluid (CSF). Thus, the proposed, although not yet validated, iCAA diagnostic criteria include decreased levels of amyloid β40 and amyloid β42 in the CSF.[1] This was derived from the diagnostic criteria for Alzheimer disease (AD).[2] Nevertheless, the specificity of CSF finding for iCAA in comparison with sCAA and AD has not been fully clarified.

Given the paucity of CSF data and the need for specific biomarkers in iCAA, the aim of this study is to review sCAA, AD, and control CSF data to differentiate CSF amyloid and τ concentrations in these different patient groups.

METHODS

Data can be made available upon reasonable request to the corresponding author.

We analyzed individual CSF concentrations of amyloid β40, amyloid β42, total τ, and phosphorylated τ 181 of patients with iCAA previously described by Pikija et al.[3] Of note, 10 of these patients were already included in a recent analysis by Pollaci and colleagues[4] and are marked with gray dots in the boxplots and scatterplots (Figure 1).

Thirty-one patients with sCAA, 28 with AD, and 30 controls previously described elsewhere[5] were considered. The Ethics Committee of the Medical Faculty of the University of Kiel, Lübeck, Tübingen, Milano, and Salzburg approved the retrospective handling of data, and individual patient consent was waived due to retrospective data analysis as previously described.[3–5]

Additionally, 2 of the authors (1 board-certified neuroradiologist [U.J.K.] and 1 board-certified neurologist [G.K.]) performed a systematic literature review in PubMed and the Cochrane or Clinical Trials database (December 4, 2023) with the search term "iCAA OR iatrogenic cerebral amyloid angiopathy OR iatrogenic-cerebral-amyloid-angiopathy" to include all patients with the following features: (1) diagnosis of iCAA according to published criteria[1] and (2) available CSF values (at least 1 of the following 4 biomarkers: amyloid β40, amyloid β42, total τ, and phosphorylated τ). If needed, corresponding authors were contacted for information.

Different analytic techniques were used for the CSF analysis in patients and iCAA. Ten samples were analyzed using the Lumipulse chemiluminescent immunoassay (FujiRebio, Tokyo, Japan) 2 samples using the cobas e 801 chemiluminescent immunoassay (Roche Diagnostics, Basel, Switzerland), 2 samples using ELISA (Innogenetics, Ghent, Belgium) and 1 sample using INNOTEST ELISA (FujiRebio). For 10 samples the analysis technique is unknown. All other samples (sCAA, AD, controls) were analyzed using the Lumipulse chemiluminescent immunoassay as previously described.[5]

The concentrations of amyloid ß40, amyloid ß42, total τand phosphorylated τwere strongly right skewed. Therefore, statistical comparisons between groups were made using a Kruskal–Wallis test followed by a pairwise Dunn test with false discovery rate adjustment for nonnormally distributed variables. All tests were 2-sided, and a *P* value of <0.05 was considered statistically significant.

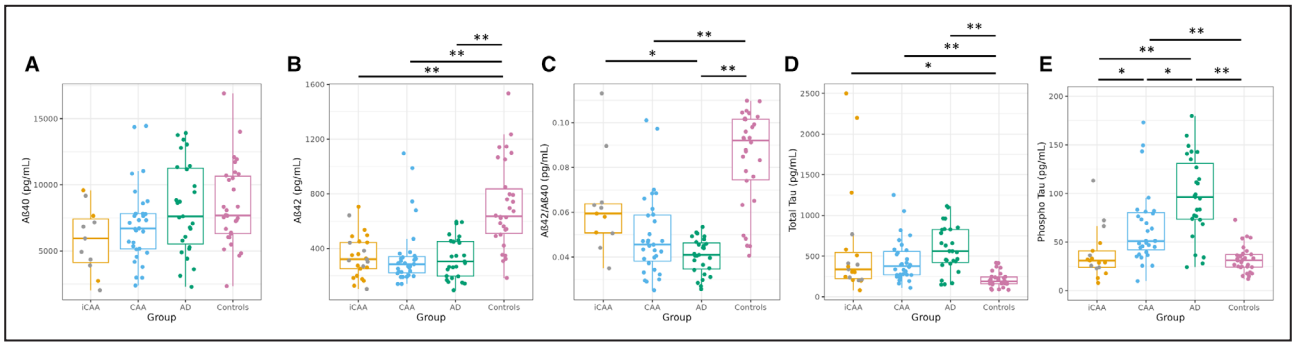

Figure 1. Boxplots and scatterplots for the diagnostic groups.
A, Amyloid β40; (**B**) amyloid β42; (**C**) amyloid β42/40 ratio; (**D**) total τ; (**E**) phosphorylated τ. *≤0.05, **<0.001. Aβ40 indicates amyloid β40; Aβ42, amyloid β42; AD, Alzheimer disease; CAA, sporadic cerebral amyloid angiopathy; and iCAA, iatrogenic cerebral amyloid angiopathy.

RESULTS

We identified 15 patients with iCAA previously described by Pikija et al[3] and 10 additional cases from 9 case descriptions from the literature[6–14] (Banerjee et al: cases 2 and 3[6]; Tachiyama et al: case 1[9]; Kellie et al: case 3,[11] Tables 1–3). Figure 2 illustrates the selection process. We found no studies in the Cochrane or Clinical Trials database.

Amyloid β40 did not differ significantly across all groups. Amyloid β42 levels were significantly higher in controls than in the other groups. Although the amyloid β42/40 ratio varied among iCAA, AD, and sCAA, with iCAA showing the highest ratio among the 3, the differences did not reach statistical significance. Total τ levels were lowest in controls but did not differ significantly between iCAA, sCAA, and AD. Phosphorylated tau levels were not statistically different in iCAA and controls, higher in sCAA, and highest in AD (Table 3, Figure 2).

DISCUSSION

In our work, CSF phosphorylated τ levels of patients with iCAA were in the same range as controls, but significantly lower than in AD and sCAA. A recent publication reported a 95% CI of phosphorylated τ between 30 pg/mL and 63 pg/mL, and thus comparable with healthy controls.[4] Our findings align with the absence of mild τ pathology observed in most but not all pathological studies of brains from patients with iCAA.[6,8,11,13]

Interestingly, although not statistically significant, amyloid β40 levels tend to be lower in iCAA and sCAA cases, and particularly in iCAA in comparison with AD and controls, suggesting that amyloid β40 could represent the biomarker of CAA[4,5] and could be particularly accumulated in patients with CAA.

Although preliminary, our results may suggest the hypothesis of a prion-like mechanism of amyloid accumulation in iCAA independently of phosphorylated τ

Table 1. Demographic, Clinical, and Radiological Characteristics and Differences Between the Diagnostic Groups

	iCAA (n=25)	sCAA (n=31)	AD (n=28)	Controls (n=30)	*P* value group differences	*P* value iCAA/sCAA	*P* value iCAA/AD	*P* value iCAA/controls	*P* value sCAA/AD	*P* value sCAA/controls	*P* value AD/controls
Age, y, mean±SD	44±11	75±5	71±8	72±8	<0.001*	<0.001‡	<0.001‡	<0.001‡	0.220‡	0.594‡	0.894‡
Female sex, n (%)	4 (16)	13 (42)	15 (55)	17 (57)	0.009+	0.425§	0.063§	0.030§	1.000§	1.000§	1.000§
ICH, n (%)	21 (76)	8 (25)	0 (0)	0 (0)	<0.001+	NA	NA	NA	NA	NA	NA
Age at exposure, y, mean±SD	8±8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cognitive impairment, n (%)	10 (40)	20 (65)	28 (100)	0 (0)	<0.001+	0.357§	<0.001§	NA	0.005§	NA	NA

AD indicates Alzheimer disease; CAA, cerebral amyloid angiopathy; iCAA, iatrogenic cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; NA, not applicable; and sCAA, sporadic cerebral amyloid angiopathy.
*ANOVA.
+Fisher exact test.
‡Tukey HSD (honestly significant difference) test.
§Pairwise-proportion test with Bonferroni *P* value adjustment.

Table 2. Demographic and Neurological Parameters of the Patients With iCAA

Reference	Sex	Age at presentation, y	Age at exposure	Cadaveric dura	ICH	Cognitive impairment
Banerjee et al, 2019, case 2[6]	Male	27	2 y	Yes	Yes	Yes
Banerjee et al, 2019, case 3[6]	Female	34	3 mo	Yes	Yes	No
Hamaguchi et al, 2019, case 1[7]	Male	30	4+7 mo	No	No (SAH)	Yes
Giaccone et al, 2019[8]	Male	29	1 y	Unconfirmed	Yes	No
Tachiyama et al, 2020[9]	Male	37	9 mo	No	Yes	Yes
Caroppo et al, 2021[10]	Male	51	17 y	Yes	Yes	No
Kellie et al, 2022, case 3[11]	Male	36	Postpartal+2 y	Yes	Yes	No
Purrucker et al, 2023[12]	Female	25	2 y	Unconfirmed	Yes	No
Jensen-Kondering et al, 2024[13]	Male	35	3 mo	Yes	Yes	No
Sezgin et al, 2024[14]	Male	41	6 mo	Unconfirmed	No	Yes
Pikija et al, 2024, case 1[3]	Male	52	12 y	No	Yes	No
Pikija et al, 2024, case 2[3]	Male	33	3 y	No	Yes	No
Pikija et al, 2024, case 3[3]	Male	55	12 y	No	No (SAH)	Yes
Pikija et al, 2024, case 4[3]	Male	70	22 y	Yes	Yes	Yes
Pikija et al, 2024, case 5[3]	Male	43	<1 y	Unconfirmed	Yes	Yes
Pikija et al, 2024, case 6[3]	Female	47	11 y	Yes	Yes	Yes
Pikija et al, 2024, case 7[3]	Male	62	22 y	Unconfirmed	Yes	No
Pikija et al, 2024, case 8[3]	Male	57	26 y	No	Yes	No
Pikija et al, 2024, case 9[3]	Male	50	7 y	Unconfirmed	Yes	Yes
Pikija et al, 2024, case 10[3]	Male	45	7 y	Unconfirmed	Yes	No
Pikija et al, 2024, case 11[3]	Male	43	4	No	No	Yes
Pikija et al, 2024, case 12[3]	Male	37	3 y	Unconfirmed	Yes	No
Pikija et al, 2024, case 13[3]	Male	40	8 y	No	Yes	No
Pikija et al, 2024, case 14[3]	Male	52	17	No	Yes	No
Pikija et al, 2024, case 15[3]	Female	60	20 y	Unconfirmed	Yes	No

iCAA and iatrogenic cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.

and coaggregation following amyloid deposition after a long incubation period.[15] However, this analysis is only exploratory and has several severe limitations. Due to the rarity of iCAA, the number of cases with published CSF data available is very limited. Pooling of data from single case reports, a cohort study and inclusion of patients from different regions, genetic backgrounds, and different underlying diseases may well have significantly biased our results. Moreover, different assays used across different sites may have influenced the results. Furthermore, it cannot be excluded that the younger age of the iCAA cases may partly explain lower phosphorylated τ values; however, this is not the case for total τ values, supporting our hypothesis. An alternative explanation for the elevated phosphorylated τ levels in sporadic CAA is the potential presence of AD

Table 3. Absolute Values of the CSF Biomarkers, Displayed as Median (Interquartile Range)

	iCAA (n=25)	sCAA (n=31)	AD (n=28)	Controls (n=30)	*P* value (Kruskal–Wallis)
Amyloid β40 (pg/mL)	5949 (3278)	6708 (2666)	7619 (5725)	7691 (4335)	0.067
Amyloid β42 (pg/mL)	321 (193)	285 (118)	305 (254)	636 (326)	<0.001
Amyloid β40/42 ratio	0.059 (0.013)	0.046 (0.021)	0.041 (0.012)	0.092 (0.027)	<0.001
Total τ (pg/mL)	337 (320)	378 (286)	561 (405)	190 (83)	<0.001
Phosphorylated τ (pg/mL)	31 (17)	51.1 (38.4)	96.4 (57.5)	31.4 (12.9)	<0.001

Significant differences between pairs are indicated Figure 1.
AD indicates Alzheimer disease; CSF, cerebrospinal fluid; iCAA, iatrogenic cerebral amyloid angiopathy; and sCAA, sporadic cerebral amyloid angiopathy.

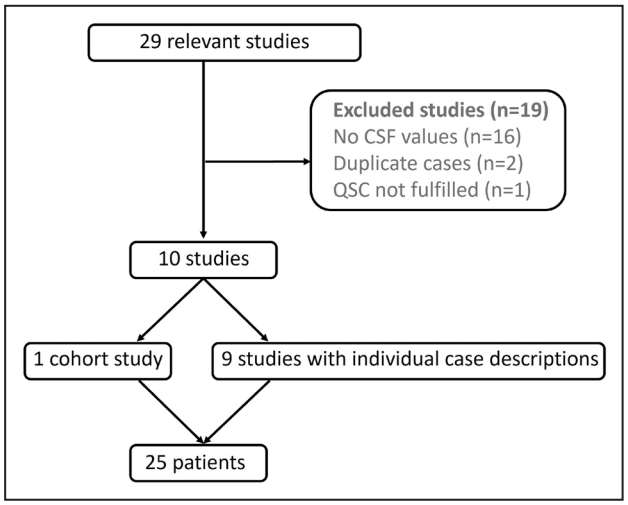

Figure 2. Study selection process for the systematic literature review.
If >1 reason for exclusion of a study was present, only the most important reason for exclusion is given. CSF indicates cerebrospinal fluid; and QSC, Queen's Square Criteria for iatrogenic cerebral amyloid angiopathy).

copathology. Notably, CAA pathology is found in up to 80% of AD autopsy cases.[16] In contrast, iCAA cases likely do not exhibit coexisting AD, given the suggested mechanism of amyloid transmission and the younger age of affected patients. This distinction may explain why phosphorylated τ levels in iCAA resemble those in healthy controls. Future data from the international registry (International Registry for Iatrogenic CAA [ucl.ac.uk]) will shed more light onto this question. These exploratory data can serve as a starting point for further studies on CSF biomarkers to establish a distinct CSF profile for iCAA, aiming to enhance the accuracy of its diagnosis.

ARTICLE INFORMATION

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