CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

CSF and Plasma Biomarkers in Patients With Iatrogenic Cerebral Amyloid Angiopathy

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Neurology® 2024;103:e209828. doi:10.1212/WNL.0000000000209828

Abstract

Objectives

Recently, a subset of patients affected by cerebral amyloid angiopathy (CAA) distinguished by atypical juvenile onset and a hypothesized iatrogenic origin (iatrogenic CAA, iCAA) has emerged. β-Amyloid (Aβ) accumulation evidenced by amyloid PET positivity or CSF Aβ decrease was included in the iCAA diagnostic criteria. Conversely, diagnostic criteria for sporadic CAA (sCAA) do not involve biomarker analysis. The aim of this study was to assess CSF and plasma levels of Aβ and tau in iCAA and sCAA cohorts.

Methods

Patients affected by probable or possible CAA according to established criteria (Boston 2.0) were prospectively recruited at Fondazione IRCCS Carlo Besta and San Gerardo dei Tintori from May 2021 to January 2024. Patients with probable and possible iCAA or sCAA with available plasma and/or CSF samples were included. Clinical and neurologic data were collected, and levels of Aβ40, Aβ42, total tau, and phospho-tau (p-tau) were assessed in CSF and plasma by SiMoA and Lumipulse.

Results

21 patients with iCAA (72% male, mean age at symptom onset 50 years [36–74]) and 32 patients with sCAA (44% male, mean age at symptom onset 68 years [52–80]) were identified. Cognitive impairment and cardiovascular risk factors in the sCAA cohort were more common compared with the iCAA cohort. Patients with sCAA and iCAA showed similar CSF levels for Aβ40 ($p = 0.5$ [sCAA, 95% CI 2,604–4,228; iCAA, 95% CI 1,958–3,736]), Aβ42 ($p = 0.7$ [sCAA, 95% CI 88–157; iCAA, 95% CI 83–155]), and total tau ($p = 0.08$ [sCAA, 95% CI 80–134; iCAA, 95% CI 37–99]). Plasma levels of Aβ40 ($p = 0.08$, 95% CI 181–222), Aβ42 ($p = 0.3$, 95% CI 6–8), and total tau ($p = 0.4$, 95% CI 3–6) were not statistically different in patients with sCAA compared with iCAA ones (Aβ40, 95% CI 153–193; Aβ42, 95% CI 6–7 and total tau, 95% CI 2–4).

Discussion

Despite presenting with a younger age at onset, fewer cardiovascular risk factors, and lower cognitive impairment, patients with iCAA demonstrated Aβ and tau levels comparable with elderly patients with sCAA, supporting a common molecular paradigm between the 2 CAA forms.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

Introduction

Recent clinical observations have highlighted several cases exhibiting clinical and radiologic features of cerebral amyloid angiopathy (CAA) but with an unexpected early onset. All cases underwent major neurosurgery or therapeutic procedures using cadaveric derived CNS tissue before 1990.[1,2] Given the conjecture of a plausible causal link with surgery, these entities have been labeled as iatrogenic CAA (iCAA). The use of β-amyloid (Aβ)–contaminated material in past neurosurgical operations is believed to have induced the deposition of Aβ into brain vessels, culminating in the onset of CAA after a latency of several decades.

Proposed iCAA diagnostic criteria encompass the reduction of Aβ levels in CSF.[3] In view of this novelty, the analysis of fluid biomarker profiles in patients affected by iCAA becomes mandatory. Conversely, biomarkers have not been considered so far for the diagnosis of sporadic CAA (sCAA).[4,5] Regrettably, to date, no studies explored this domain. The aim of this study was to assess CSF and plasma Aβ and tau levels in iCAA and to compare them with sCAA.

Methods

Consecutive patients affected by probable or possible CAA according to established criteria (Boston 2.0)[4] were prospectively recruited at Fondazione IRCCS Carlo Besta (Milan, Italy) and Fondazione IRCCS San Gerardo dei Tintori (Monza, Italy) from May 2021 to January 2024. Of these patients, those with a diagnosis of probable and possible iCAA and sCAA with available plasma and/or CSF samples were included. The diagnosis of possible or probable iCAA was performed according to previously proposed criteria.[3] Lumbar puncture was performed when there was clinical indication for CSF analysis (e.g., reported or actual cognitive symptoms and exclusion of differential diagnoses), cerebral hemorrhage had occurred at least 2 months before, the patient gave signed informed consent for the procedure, and contraindications were ruled out to lumbar puncture. All patients underwent brain MRI and amyloid PET. Peripheral blood-EDTA and CSF were collected during diagnostic procedures. *PSEN1*, *PSEN2*, *APP*, and *APOE* gene screening was performed in all patients with iCAA. The study design was approved by the Ethics Committee for SENECA (NCT04204642, October 21, 2020),[6] in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients for data and biological sample collection, and measures to safeguard patient confidentiality were rigorously implemented.

CSF concentrations of Aβ40, Aβ42, total tau, and p-tau181 were determined through Lumipulse G600II (Fujirebio, Ghent, Belgium). The quantitative determination of Aβ40, Aβ42, and total tau in CSF and plasma was performed by SiMoA on the SR-X platform using the N3PA Advantage Kit (Quanterix, Billerica, MA).[7]

Clinical/biological data were expressed as mean or median ±SD, and statistical significance was determined using the χ^2 test or nonparametric Mann-Whitney *U* test by GraphPadPrism8 (GraphPad Software, Inc., San Diego, CA). $p < 0.05$ was considered statistically significant. Our analysis is affected by an effect size from small to moderate according to Cohen *D*.

Data not provided in the article because of space limitations may be shared anonymized at the request of any qualified investigator for purposes of replicating procedures and results.

Results

We identified 21 patients with probable iCAA (72% male) and 32 control patients with sCAA of probable grade according to Boston 2.0 criteria (44% male). None of the cases of sCAA had a history of significant head trauma or neurosurgical interventions. All patients with iCAA had positive amyloid PET scan, and none had variation in the *APP*, *PSEN1*, and *PSEN2* genes, nor *APOE* ε4 alleles. All neurosurgical procedures were conducted before 1990. Previous major trauma leading to surgery was reported in 10 cases of iCAA (47.6%). Mean age at first symptoms was significantly lower in iCAA than in sCAA (50 ± 9 years vs 68 ± 7 years), and the diagnostic latency (i.e., time between onset and diagnosis) was longer in iCAA than in sCAA (5 ± 5 years vs 2 ± 2 years). Cognitive impairment, identified with a score lower than 24 at the Mini-Mental State Examination Test, resulted significantly more common in the sCAA group ($p < 0.004$). Cardiovascular risk factors were prevalent in the sCAA group, although without reaching statistical significance. The results are summarized in Table 1.

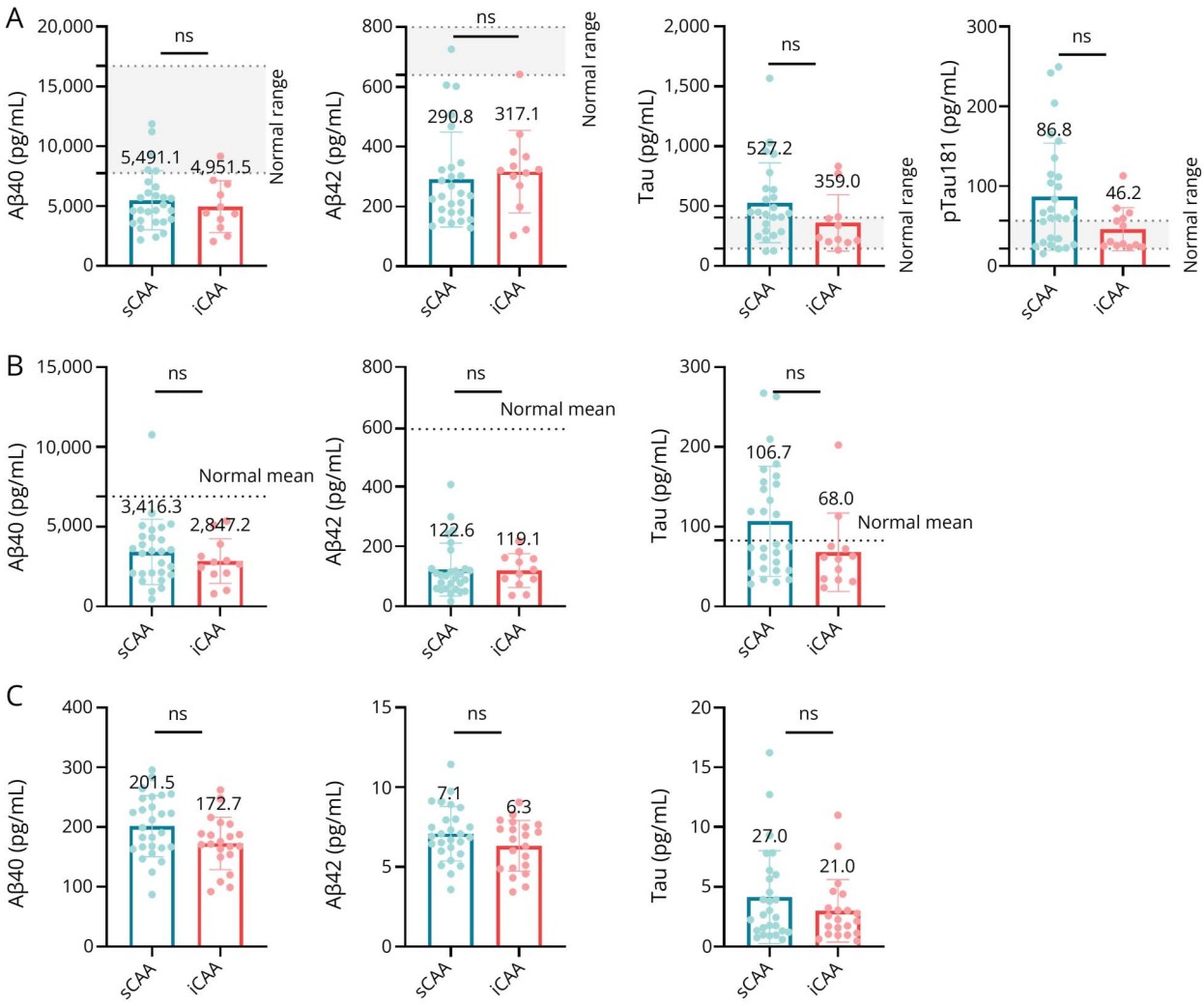
Evaluation of Aβ40 ($p = 0.61$), Aβ42 ($p = 0.28$), total tau ($p = 0.06$), and p-tau181 ($p = 0.06$) levels in CSF using Lumipulse did not reveal significant differences between patients with iCAA and sCAA (Figure, A, Table 2). Similar findings were confirmed through SiMoA analysis for Aβ40 ($p = 0.52$), Aβ42 ($p = 0.72$), and total tau ($p = 0.08$) concentrations (Figure, B, Table 2). A slight reduction of tau levels in CSF of patients with iCAA was observed, without but close to a statistical significance if compared with patients with sCAA. Sex or number of years since the neurologic procedure did not influence CSF level of amyloid and tau. Analysis of plasma Aβ40 ($p = 0.09$), Aβ42 ($p = 0.26$), and total tau ($p = 0.4$) levels through SiMoA yielded comparable results between iCAA and sCAA groups (Figure, C, Table 2).

Table 1 sCAA and iCAA Clinical Characteristics

	sCAA (n = 32)	iCAA (n = 21)	*p* Value	
Demographic features				
Age at first clinical evaluation, y, mean ± SD (range)	70 ± 7 (53–80)	55 ± 9 (39–67)	<0.0001	****
Age at first presentation, y, mean ± SD (range)	68 ± 7 (52–80)	50 ± 9 (36–74)	<0.0001	****
Latency between neurosurgery and onset, y, mean ± SD	—	37 ± 6	—	
Latency between onset and diagnosis, y, mean ± SD	2 ± 2	5 ± 5	0.0091	**
Latency between last ICH and LP, mo, median ±SD (range)	11 ± 30 (2–113)	10 ± 13 (3–36)	0.6101	ns
Sex				
Female	18 (56)	6 (28)	0.0477	*
Male	14 (44)	15 (72)		
Neurosurgery before 1990, n (%)				
Cerebral	—	16 (76)	—	
Spinal	—	5 (23)	—	
Surgery due to trauma	—	10 (48)	—	
Confirmed cadaveric dura	—	9 (43)	—	
Onset symptom, n (%)				
ICH	17 (53)	10 (48)	0.4646	ns
TIA	4 (13)	3 (14)	0.8510	ns
Seizures	2 (6)	1 (5)	0.8186	ns
Cognitive impairment (reported or actual)	6 (19)	0 (0)		
TFNE	1 (3)	6 (29)	0.0074	**
SAH	2 (6)	1 (5)	0.8186	ns
Cardiovascular risk factors, n (%)				
Hypertension	19 (59)	9 (43)	0.2387	ns
Dyslipidemia	17 (53)	9 (43)	0.4645	ns
Diabetes	4 (13)	1 (5)	0.3458	ns
Smokers	11 (34)	4 (19)	0.2256	ns
Radiologic features				
Lobar ICHs n (%)	19 (59)	12 (57)	0.8719	ns
No. of lobar ICHs, mean (range)	3 (0–8)	3 (0–10)	0.4122	ns
Lobar CMBs n (%)	29 (91)	16 (76)	0.1511	ns
No. of lobar CMBs, mean (range)	34 (3–100)	39 (4–300)	0.4237	ns
cSS, n (%)	24 (75)	20 (95)	0.0549	ns
WMHs, n (%)	28 (88)	17 (81)	0.5149	ns
CPS-PVS, n (%)	24 (75)	6 (29)	0.0009	***
Any SAH, n (%)	3 (9)	3 (14)	0.5810	ns
Cognition assessment				
Cognitive impairment (MMSE)	17 (53)	3 (14)	0.0043	**

Abbreviations: CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; CPS-PVS = centrum semiovale enlarged perivascular spaces; cSS = cortical superficial siderosis; iCAA = iatrogenic CAA; ICH = intracerebral hemorrhage; LP = lumbar puncture; MMSE = Mini-Mental State Examination; SAH = subarachnoid hemorrhage; sCAA = sporadic CAA; TFNE = transient focal neurologic episodes; TIA = transient ischemic attack; WMH = white matter hyperintensity. Statistical significance was calculated through the nonparametric Mann-Whitney *U* test or χ^2 test. *p* Values <0.05 were considered statistically significant.

Figure Lumipulse CSF (A), SiMoA CSF (B), and SiMoA Plasma (C) Analysis



CSF concentrations of Aβ40, Aβ42, tau, and p-tau of patients with sCAA and iCAA were evaluated by Lumipulse G1200 (A) and SiMoA SRX (B) and expressed as pg/mL as indicated. (C) Plasma concentrations of Aβ40, Aβ42, and tau of patients with sCAA and iCAA were determined by SiMoA and expressed as pg/mL, as indicated. The number above bars indicates the means, and the error bars represent the SD. Each spot indicates an individual data point. Reference values of control patients are reported in light gray and indicated as "normal range"[10,11] or "normal mean,"[9,12] respectively. The statistical significance was calculated through the nonparametric Mann-Whitney *U* test. *p* Value <0.05 was considered statistically significant (ns; not significant). CAA = cerebral amyloid angiopathy; iCAA = iatrogenic CAA; sCAA = sporadic CAA.

Discussion

This study investigates neurodegenerativebiomarkers, in both CSF and blood, in patients with iCAA. Notably, patients with iCAA, in contrast to sCAA, exhibited a younger age and a higher proportion of men, consistent with previous observations.[1,2] The longer latency between symptom onset and diagnosis in iCAA was probably due to the recent description of the entity, the rarity of the disease, and the atypical young age at onset. In addition, patients with iCAA presented slightly less cardiovascular risk factors and lower cognitive impairment. Nevertheless, plasma and CSF amyloid levels were comparable between patients with iCAA and elderly patients with sCAA. Because elevated tau in plasma and CSF was observed after brain trauma, even at long distance from its occurrence,[8] we might have anticipated higher tau levels in our patients with iCAA. However, CSF tau levels, although without statistical significance, seemed slightly inferior in patients with iCAA than in those with sCAA. This could be due to the younger mean age of patients with iCAA. Indeed, if compared with a control group of a similar age,[9] tau level results are comparable.

Reference values for amyloid and tau in CSF of control patients are available for both Lumipulse (7,755–16,715 pg/mL for Aβ40, >640 pg/mL for Aβ42, 21.5–56.5 pg/mL for p-tau181)[10,11] and SiMoA (Aβ40 = 6,898 pg/mL, Aβ42 = 592 pg/mL, tau = 82.5 pg/mL).[9,12] Regarding plasma, cutoff values for controls are not yet established; to date, previous works have given discordant values of Aβ40, Aβ42, and tau.[13,14] Compared with reference values, a decrease in amyloid biomarker levels was noted in the CSF of each cohort.

Table 2 CSF and Plasma Biomarker Concentration

Analysis method		sCAA		iCAA		*p* Value
		Mean ± SD (pg/mL)	95% CI	Mean ± SD (pg/mL)	95% CI	
CSF						
Lumipulse	Aβ40	5,491.1 ± 2,468	4,515–6,467	4,951.5 ± 2,160	3,501–6,402	0.612
	Aβ42	290.8 ± 159	228–354	317.1 ± 138	234–401	0.277
	Tau	527.2 ± 333	386–668	359.0 ± 235	201–517	0.055
	p-tau181	86.8 ± 67	60–113	46.2 ± 27	30–63	0.064
SiMoA	Aβ40	3,416.3 ± 2,052	2,604–4,228	2,487.2 ± 1,399	1,958–3,736	0.518
	Aβ42	122.6 ± 88	88–157	119.1 ± 56	83–155	0.716
	Tau	106.7 ± 49	80–134	68 ± 49	37–99	0.079
Plasma						
SiMoA	Aβ40	201.5 ± 51	181–222	172.7 ± 44	153–193	0.088
	Aβ42	7.1 ± 2	6–8	6.3 ± 2	6–7	0.255
	Tau	4.1 ± 4	3–6	3.0 ± 3	2–4	0.409

Abbreviations: CAA = cerebral amyloid angiopathy; iCAA = iatrogenic CAA; sCAA = sporadic CAA.
CSF and plasma concentrations of Aβ40, Aβ2, tau, and phospho-tau of patients with sCAA and iCAA were evaluated by Lumipulse G 1200 and SiMoA SRX and expressed as pg/mL, as indicated. The statistical significance was calculated using the nonparametric Mann-Whitney *U* test. *p* Value <0.05 was considered statistically significant.

Findings support the hypothesis that iCAA and sCAA share a common biomarker profile despite a distinct etiology. Since amyloid levels are correlated with aging, higher values would have been expected in older patients with sCAA. However, the results are not different when comparing the two groups.

Some limitations should be acknowledged. First, the sample size was small due to the actual rarity of the disease.[15] Second, a possible selection bias can be hypothesized because of the nature of the participating centers, both highly specialized and focused on CAA management. Third, a control cohort was absent. Finally, although clinical and radiologic features of our cohort align with CAA, a potential inclusion of patients with mixed CAA/AD features has to be acknowledged, as expression of the neuropathologic continuum linking the 2 conditions.

Our findings underscore the importance of conducting further investigations in larger populations to explore amyloid and tau levels in CSF and plasma, to improve the diagnostic process and criteria for both iCAA and sCAA.

Acknowledgment

The authors thank all Italian citizens who allocated 5 × 1,000 income tax to support the Fondazione IRCCS Istituto Neurologico "Carlo Besta" and project RC19.1 PRIORITY.

Study Funding

This work was partially supported also by Ministero della Salute (Ricerca Corrente 2022–2024 to A.B. and L.G.).

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* March 28, 2024. Accepted in final form July 5, 2024. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

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