Risk of Seizures Among Patients with Cerebral Amyloid Angiopathy – a Nationwide Retrospective Cohort Study in the United States

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Key Points

- **Patients with cerebral amyloid angiopathy (CAA) were approximately 9 and 11 times more likely to experience seizures and status epilepticus, respectively, than matched controls without CAA in this large retrospective cohort study (Figure 1).**
- **Increased risk is observed after accounting for medical history, including prior intracerebral hemorrhage (ICH), and when stratifying by prior seizure history.**
- **These findings suggest that seizure may be an underappreciated clinical manifestation of CAA, beyond its cardinal clinical presentations.**

Background and Objective

Background

- CAA is a progressive neurovascular disease caused by amyloid-beta deposition in the cerebral vasculature.
- Emerging evidence suggests that its clinical spectrum extends beyond hemorrhagic stroke to include cognitive and functional decline, as well as seizures.
- Risk of seizures in patients with CAA remains poorly characterized.[1]

Objective

- To estimate the risk of seizure in patients with CAA versus age- and sex-matched CAA-free controls, and to identify risk factors associated with seizure in CAA.

Methods

Study Design

- Retrospective cohort study using data from an administrative claims database of US Medicare Advantage and commercial insurance beneficiaries.
  - Patients with CAA : >50 years old; ≥1 physician encounter with ICD-10 code I68.0 from 2017 to 2024; 12 months of continuous enrollment.
  - Controls: age- and sex-matched, CAA-free, 1:4 ratio.

Study Outcomes

- Primary: seizure, ascertained using a set of validated ICD-10 codes for seizure from inpatient or emergency department encounter.
- Secondary: hospitalization with status epilepticus.

Data Analysis

- Descriptive statistics of patient characteristics.
- Poisson regression for incidence rates with 95% confidence intervals (CIs).
- Crude and adjusted* Cox proportional hazard regression with 95% CIs to assess association between CAA and seizure risk compared with controls, stratified by history of seizure (based on diagnoses and medication use data).

*Adjusted for ICH (which included non-cortical hemorrhagic stroke), kidney disease, and liver disease, chosen on the basis of known strong association with the outcome of seizure.

Results

Demographics and Clinical History (Table 1)

- 7294 patients with CAA and 29 176 matched controls were identified.
- Median age was 77 years (Q1: 72, Q3: 82) and median follow-up was 29.4 months (Q1: 12.3, Q3: 56.8).
- Patients with CAA had higher prevalence of prior ICH (32.4% vs 0.5%) and seizure (18.7% vs 1.8%) versus matched controls.

Table 1. Distribution of Baseline Demographic and Clinical Characteristics

Baseline Characteristics	Patients with CAA	Matched Controls
Patients, n	7294	29 176
Age on index date, years, n (%)		
50–59	112 (1.5)	448 (1.5)
60–69	931 (12.8)	3724 (12.8)
70–79	3327 (45.6)	13 308 (45.6)
80+	2924 (40.1)	11 696 (40.1)
Female, n (%)	3914 (53.7)	15 656 (53.7)
Insurance type, n (%)		
Commercial	399 (5.5)	4641 (15.9)
Medicare	6889 (94.4)	24 488 (83.9)
Both	6 (0.1)	47 (0.2)
Medical history of, n (%)		
ICH	2364 (32.4)	143 (0.5)
Seizure	1361 (18.7)	538 (1.8)
Seizure treatment		
Medications	1388 (19.0)	923 (3.2)
Neuromodulation	64 (0.9)	244 (0.8)
Diabetes	2105 (28.9)	7826 (26.8)
Hypertension	6169 (84.6)	21 659 (74.2)
Dementia	2839 (38.9)	1970 (6.8)
Liver disease	400 (5.5)	977 (3.3)
Kidney disease	297 (4.1)	795 (2.7)

CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage.

Seizure Incidence (Table 2)

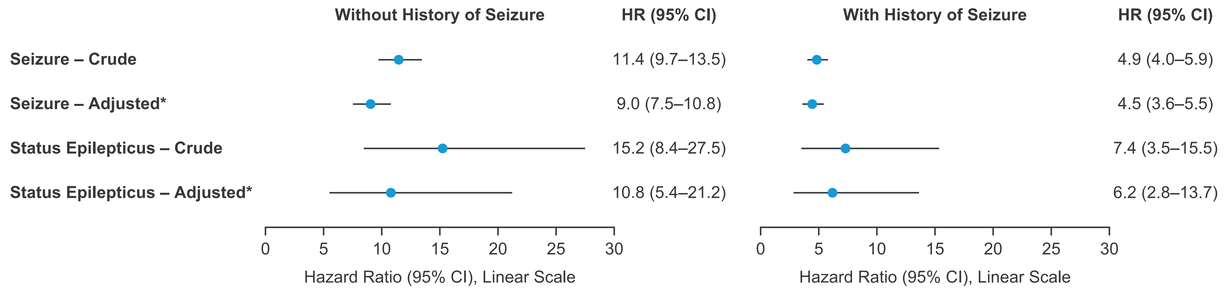
- Incidence of seizure in patients without history of seizure/epilepsy was 4.0 and 0.3 per 100 person-years in patients with CAA and in matched controls, respectively.
- Increased risk was observed when stratified by history of ICH; the incidence rate ratios were 7 and 14 comparing patients with CAA with controls, among those with and without ICH history, respectively.

Table 2. Incidence Rate and Incidence Rate Ratio of Seizure in Patients with CAA and Matched Controls

	Patients with CAA			Matched Controls			Incidence Rate Ratio
	Patients, n	Seizure Events, n*	Incidence Rate per 100 PY (95% CI)	Controls, n	Seizure Events, n*	Incidence Rate per 100 PY (95% CI)	
Overall	7294	987	8.1 (7.6–8.6)	29 176	406	0.4 (0.4–0.5)	19
Age group, years							
50–59	112	17	10.5 (6.5–16.9)	448	0	–	–
60–69	931	170	11.1 (9.6–12.9)	3724	31	0.3 (0.2–0.4)	38
70–79	3327	470	8.0 (7.3–8.8)	13 308	198	0.4 (0.3–0.5)	20
80+	2924	330	7.1 (6.4–7.9)	11 696	177	0.5 (0.5–0.6)	14
History of seizure							
Yes	1361	559	34.9 (32.1–37.9)	538	110	8.2 (6.8–9.9)	4
No	5933	428	4.0 (3.7–4.4)	28 638	296	0.3 (0.3–0.4)	13
History of ICH							
Yes	2364	500	13.6 (12.5–14.8)	143	7	2.0 (1.0–4.2)	7
No	4930	487	5.7 (5.2–6.3)	29 033	399	0.4 (0.4–0.5)	14

*Seizure event is defined as emergency department or inpatient encounter with a seizure diagnosis.
CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; PY, person-years.

Figure 1. Hazard Ratio of Seizure and Status Epilepticus Comparing Patients with CAA with Matched Controls



*Adjusting for ICH, kidney disease, and liver disease, matched on age and sex.
CAA, cerebral amyloid angiopathy; HR, hazard ratio; ICH, intracerebral hemorrhage.

REFERENCE

1. Freund BE *et al. Neurol Clin Pract* 2025;15:e200454.

DISCLOSURES

NSP, **JZ**, **AA**, **LF**, **VK**, and **JS** are employees of and shareholders in Alnylam Pharmaceuticals. **ML** has no conflicts to report.

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