Epilepsy Currents
2024, Vol. 24(2) 93-95

DOI: 10.1177/15357597231225059
journals.sagepub.com/home/epi
Sage

The Winners of the Cerebral Amyloid Angiopathy Epilepsy Prize Are: Blood and Inflammation

Epilepsy in Cerebral Amyloid Angiopathy: An Observational Retrospective Study of a Large Population

Tabaee Damavandi P, Storti B, Fabin N, Bianchi E, Ferrarese C, DiFrancesco JC. *Epilepsia*. 2023;64(2):500-510. doi:10.1111/epi.17489

Objective: Cerebral amyloid angiopathy (CAA) is a major cause of spontaneous intracranial hemorrhage in older adults. Epilepsy represents a possible sequela of the disease. To date, studies on epilepsy in CAA are lacking, and the few data available mainly focus on CAA-related inflammation (CAA-ri), the inflammatory form of the disease. Methods: In this retrospective observational study, we consecutively recruited CAA patients observed over a time span of 10 years, collecting demographic, clinical, and instrumental data. Significant baseline characteristics were evaluated as potential risk factors for the development of epilepsy in the CAA population, and in the subgroups of CAA-ri and CAA without inflammatory reaction (CAA-nri). The effect of potential risk factors for epilepsy was measured as odds ratio with 95% confidence interval. Results: Within 96 recruited CAA cases, 33 (34.4%) developed epilepsy during follow-up (median = 13.5 months). The prevalent type of seizure was focal (81.3%); 12.1% of the epileptic patients presented status epilepticus, and 6.1% developed drug-resistant epilepsy. Electroencephalographic traces revealed slow and epileptic discharge activity in the majority of epileptic patients, but also in those without epilepsy. The presence of focal or disseminated cortical superficial siderosis (cSS) was associated with an increased risk of epilepsy in the CAA-nri group, and the association with CAA-ri and epilepsy was present in the overall population. Significance: Epilepsy is a common manifestation during the course of CAA, where CAA-ri and cSS represent predisposing factors for the development of seizures. These data suggest the importance of a deep characterization of CAA patients, to better select those more prone to develop epilepsy.

Commentary

Cerebral amyloid angiopathy (CAA) is a cerebrovascular disorder characterized by amyloidβ deposition in the cerebral blood vessels. It is associated with transient focal neurologic episodes (TFNE), lobar intracranial hemorrhage (ICH), non-traumatic subarachnoid hemorrhage (SAH), and cognitive impairment.[1] The prevalence of CAA in cognitively normal elderly individuals is 5% to 7% but in the setting of Alzheimer's disease the prevalence is 3-fold higher.[2] Seizures have been described as a complication of CAA mostly in the setting of acute ICH.[3] Given how common this disease is in the elderly population, one would expect an increase in incidence and prevalence of CAA-related seizures. However, studies examining the prevalence of epilepsy and epilepsy-related outcomes have been limited.

In the current study,[4] a cohort of retrospectively identified patients diagnosed with CAA over a 10-year period in a single Center, San Gerardo, in Italy was identified. The diagnosis of CAA was made based on the newly released Boston 2.0 criteria[5] which rely heavily on MRI features suggestive of CAA. The MRIs were reviewed for features of small vessel disease and a global score was generated based on cerebral microbleeds (CMB), cortical superficial siderosis (cSS), white matter hyperintensities (WMH), and centrum semiovale enlarged perivascular spaces. The charts were also reviewed to determine the seizure prevalence in the cohort after diagnosis, the prevalence of epilepsy, and the long-term seizure outcomes. Multivariate logistic regression models were used to identify predictors of the development of epilepsy in the setting of CAA.

The cohort consisted of 96 patients, 94 of them were probable CAA and 2 were possible CAA. Twenty-five out of 96 had CAA-related inflammation (CAA-ri), while the others were categorized as CAA without inflammatory reaction (CAA-nri). There was a high prevalence of epilepsy, 33.4%, with 28.2% in the CAA-nri group and 52% in the CAA-ri group. Notably 5 patients presented with status epilepticus, 2 in the setting of an ICH. The overall prevalence of epileptiform abnormalities in the cohort was 25%. The rate of drug-resistant epilepsy was low at 6.1%. In terms of predictors of

developing epilepsy, the presence of CAA-ri conferred an odds ratio of 3.18 (95% CI 1.08-9.38), while in the CAA-nri group the presence of cSS conferred an odds ratio of 6.08 (95% CI 1.25-29.49). Surprisingly, a higher load of cortical microbleeds was observed in the group without epilepsy.

Cerebral amyloid angiopathy is a very informative disease to study from an epilepsy perspective given that several of its pathologic features are pro-epileptogenic. First there is the obvious risk factor of lobar ICH, but also other bleeding insults such as cSS, nonaneurysmal SAH, and CMBs and the resulting pro-epileptic blood-related products and hemosiderin deposits. It is thus not surprising that the patients with cSS had a higher risk of seizures, and that was the only predictor that was significant. We know from studies in stroke and SAH that patients with ICH[6] or SAH have a higher risk of epilepsy as compared to patients with ischemic stroke. It is surprising that CMBs were in fact more predominant in the group without a history of seizures that could be due to their predominance in cortical regions that are less likely to cause seizures (occipital, cerebellar locations) in the non-epilepsy group. This was not an aspect that was evaluated in the study. There was a trend for patients with ICH as well to develop epilepsy (19/20 vs 40/51) but this did not reach statistical significance.

Other than blood, inflammation was also associated with the risk of epilepsy, with more than half of patients with CAA-ri developing epilepsy. CAA-related inflammation is characterized by prominent inflammation usually with mass effect with a predilection to the frontal and temporal lobes, and acute symptomatic seizures ultimately requiring treatment with steroids. This study confirms our suspicions that any process leading to cortical inflammation and edema is likely to trigger not only acute seizures but also place someone at risk of epilepsy. The other pathologic features that were investigated included white matter ischemic disease and enlarged perivascular spaces.[1] Late onset epilepsy has been linked to a higher burden of WMHs[7] which may reflect increased blood–brain barrier permeability. Alternatively, some of these WMHs could strategically disconnect regions of the temporal lobe and render them epileptogenic. The newest additions to the Boston criteria are the enlarged perivascular spaces indicating impairments in the glymphatic system. The link to seizures could be that there is impaired clearance of neurotoxic materials. Finally, patients can have coexisting Alzheimer's disease pathology and CAA, and thus could have seizures due to parenchymal buildup of the pro-epileptogenic proteins phosphorylated tau and amyloid β-42.[8]

The authors must be commended for being the first to systematically review the neuroimaging features of CAA and linking them to epilepsy. There are several limitations to their approach, the most significant being their reliance on retrospective data. For example, the epilepsy group was more likely to undergo an EEG study, and to be followed longer. It is also unclear whether the EEGs were routine or prolonged EEG, and whether they were ordered in the inpatient setting or in the outpatient setting. It would have also been helpful to provide further information on the acute symptomatic seizures and whether they were a predictor of subsequent development of epilepsy. There is also the difficult task of differentiating TFNE from seizures,[9] with the former lasting longer, associated with negative symptoms, and linked to cortical spreading depression. The good news is that only 2 patients from the cohort were drug resistant. This is a finding that should give us pause, why would a brain that is so laden with multiple epileptogenic lesions be so drug responsive? It could be that we are missing subtle seizures in this population given their age, and the lower prevalence of convulsive seizures. Or they are truly drug responsive and their disrupted blood–brain barrier is allowing the drug to have better access to the brain and become more effective, alternatively the nature of the connectivity of the epileptogenic lesion to the rest of the brain might be different in CAA-related epilepsy/the older brain.

Another thing to keep in mind is that in addition to the naturally occurring CAA with aging, we will also be seeing a new wave of iatrogenic-induced CAA with the advent of anti-amyloid antibodies. These are largely considered to be asymptomatic and are termed amyloid-related imaging abnormalities (ARIA) which could either include -E (edema) or -H (hemorrhage). Notably, seizures have not been described as a common complication of ARIA in phase 3 clinical trials when the data were published.[10] In the real world, when strict patient selection is no longer the case, this might no longer hold. It is time to further delve into the link between cerebrovascular disease and seizures. There is much for us to learn.

Rani A. Sarkis, MD, MSc
Epilepsy Division, Department of Neurology,
Brigham and Women's Hospital, Harvard Medical School

ORCID iD

Rani A. Sarkis https://orcid.org/0000-0001-8291-7864

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Gatti L, Tinelli F, Scelzo E, et al. Understanding the pathophysiology of cerebral amyloid angiopathy. *Int J Mol Sci*. 2020;21(10):3435.
2. Jäkel L, De Kort AM, Klijn CJM, Schreuder FHBM, Verbeek MM. Prevalence of cerebral amyloid angiopathy: a systematic review and meta-analysis. *Alzheimers Dement*. 2022;18(1):10-28.
3. Nagaraja N, Narayana Reddy VB. Prevalence of concomitant neurological disorders and long-term outcome of patients hospitalized for intracerebral hemorrhage with versus without cerebral amyloid angiopathy. *Neurocrit Care*. 2023:1-9. doi:10.1007/S12028-023-01753-X
4. Tabaee Damavandi P, Storti B, Fabin N, Bianchi E, Ferrarese C, DiFrancesco JC. Epilepsy in cerebral amyloid angiopathy: an observational retrospective study of a large population. *Epilepsia*. 2023;64(2):500-510. doi:10.1111/epi.17489

5. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol*. 2022;21(8):714-725.
6. Lahti AM, Saloheimo P, Huhtakangas J, et al. Poststroke epilepsy in long-term survivors of primary intracerebral hemorrhage. *Neurology*. 2017;88(23):2169-2175.
7. Johnson EL, Krauss GL, Lee AK, et al. Association between white matter hyperintensities, cortical volumes, and late-onset epilepsy. *Neurology*. 2019;92(9): E988-E995.
8. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease—one peptide, two pathways. *Nat Rev Neurol*. 2020;16(1):30-42.
9. Smith EE, Charidimou A, Ayata C, Werring DJ, Greenberg SM. Cerebral amyloid angiopathy-related transient focal neurologic episodes. *Neurology*. 2021;97(5):231-238.
10. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol*. 2022;79(1):13-21.