Original Investigation

Validation of Clinicoradiological Criteria for the Diagnosis of Cerebral Amyloid Angiopathy–Related Inflammation

Eitan Auriel, MD, MSc; Andreas Charidimou, MD, PhD; M. Edip Gurol, MD, MSc; Jun Ni, MD; Ellis S. Van Etten, MD; Sergi Martinez-Ramirez, MD; Gregoire Boulouis, MD; Fabrizio Piazza, PhD; Jacopo C. DiFrancesco, MD, PhD; Matthew P. Frosch, MD, PhD; Octávio M. Pontes-Neto, MD, PhD; Ashkan Shoamanesh, MD; Yael Reijmer, PhD; Anastasia Vashkevich, BA; Alison M. Ayres, BA; Kristin M. Schwab, BA; Anand Viswanathan, MD, PhD; Steven M. Greenberg, MD, PhD

IMPORTANCE Cerebral amyloid angiopathy–related inflammation (CAA-ri) is an important diagnosis to reach in clinical practice because many patients with the disease respond to immunosuppressive therapy. Reliable noninvasive diagnostic criteria for CAA-ri would allow some patients to avoid the risk of brain biopsy.

OBJECTIVE To test the sensitivity and specificity of clinical and neuroimaging-based criteria for CAA-ri.

DESIGN, SETTING, AND PARTICIPANTS We modified the previously proposed clinicoradiological criteria and retrospectively analyzed clinical medical records and magnetic resonance imaging fluid-attenuated inversion recovery and gradient-echo scans obtained from individuals with CAA-ri and noninflammatory CAA. At 2 referral centers between October 1, 1995, and May 31, 2013, and between January 1, 2009, and December 31, 2011, participants included 17 individuals with pathologically confirmed CAA-ri and 37 control group members with pathologically confirmed noninflammatory CAA. The control group was further divided into those with past lobar intracerebral hemorrhage (ICH) (n = 21) and those with cerebral microbleeds only and no history of ICH (n = 16). The dates of our analysis were September 1, 2012, to August 31, 2015.

MAIN OUTCOMES AND MEASURES The sensitivity and specificity of prespecified criteria for probable CAA-ri (requiring asymmetric white matter hyperintensities extending to the subcortical white matter) and possible CAA-ri (not requiring the white matter hyperintensities to be asymmetric).

RESULTS The 17 patients in the CAA-ri group were a mean (SD) of 68 (8) years and 8 (47%) were women. In the CAA-ri group, 14 of 17 (82%) met the criteria for both probable and possible CAA-ri. In the control group having noninflammatory CAA with lobar ICH, 1 of 21 (5%) met the criteria for possible CAA-ri, and none met the criteria for probable CAA-ri. In the control group having noninflammatory CAA with no ICH, 11 of 16 (69%) met the criteria for possible CAA-ri, and 1 of 16 (6%) met the criteria for probable CAA-ri. These findings yielded a sensitivity and specificity of 82% and 97%, respectively, for the probable criteria and a sensitivity and specificity of 82% and 68%, respectively, for the possible criteria.

CONCLUSIONS AND RELEVANCE Our data suggest that a reliable diagnosis of CAA-ri can be reached from basic clinical and magnetic resonance imaging information alone, with good sensitivity and excellent specificity.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Steven M. Greenberg, MD, PhD, The J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, 175 Cambridge St, Ste 300, Boston, MA 02114 (sgreenberg@partners.org).

JAMA Neurol. 2016;73(2):197-202. doi:10.1001/jamaneurol.2015.4078
Published online December 28, 2015.

Cerebral amyloid angiopathy–related inflammation (CAA-ri) is a disease subtype characterized by rapidly progressive cognitive decline, seizures, headaches, T2-weighted hyperintense magnetic resonance imaging (MRI) lesions, and neuropathological evidence of CAA-associated vascular inflammation.[1-3] In the recent past, CAA-ri has generated additional interest for its clinicoradiological similarities to the amyloid-related imaging abnormalities[4,5] developed by a subset of patients with Alzheimer disease receiving bapineuzumab, an experimental humanized, monoclonal antibody to β-amyloid.[4,5] Cerebral amyloid angiopathy–related inflammation is an important diagnosis to reach in clinical practice because many patients with the disease respond to immunosuppressive therapy. However, definitive diagnosis of CAA-ri generally requires brain biopsy, highlighting the importance of developing noninvasive diagnostic criteria.[6] Some criteria for the diagnosis of probable CAA-ri using clinical and MRI data have been proposed[3] but not yet validated.

In the present study, we tested the sensitivity and specificity of the modified criteria for probable and possible CAA-ri in groups of individuals with histologically proven CAA-ri and noninflammatory CAA. Because the primary goal for such criteria is to spare at least some patients with CAA-ri from the morbidity of unnecessary brain biopsy, we sought to identify the criteria that would be as sensitive as possible for CAA-ri while maintaining close to 100% specificity.

Methods

Diagnostic Criteria

According to the previously suggested criteria by Chung et al,[3] the diagnosis of probable CAA-ri requires the following 4 findings: (1) presentation with a variable combination of acute or subacute onset of headache, decrease in consciousness or behavioral change, focal neurological deficits, and seizures; (2) MRI with patchy or confluent T2-weighted or fluid-attenuated inversion recovery (FLAIR) lesions, usually asymmetric, with or without mass effect and with or without leptomeningeal or parenchymal enhancement; (3) multiple lobar microhemorrhages and recent or past lobar intracerebral hemorrhage (ICH); and (4) the absence of neoplastic, infectious, or other cause. We further refined and operationalized these criteria to reflect previous experience with the clinical presentation, specific pattern of white matter hyperintensity (WMH) distribution, and superficial siderosis as a type of bleeding manifestation of CAA.[7] Therefore, the modified criteria tested herein (**Table 1**) specify the following: (1) clinical symptoms, such as headaches or decrease in consciousness, could occur over longer time frames (ie, chronic, as well as acute or subacute); (2) WMH patterns would be asymmetric and extend to the immediately subcortical white matter (to meet the more stringent criteria for probable CAA-ri) or simply extend to the immediately subcortical white matter (possible CAA-ri) (**Figure 1**); and (3) the appearance of superficial siderosis would be counted as 1 bleeding manifestation for CAA. For the purposes of the present validation study, these modified criteria were prespecified before the current data review.

Study Population

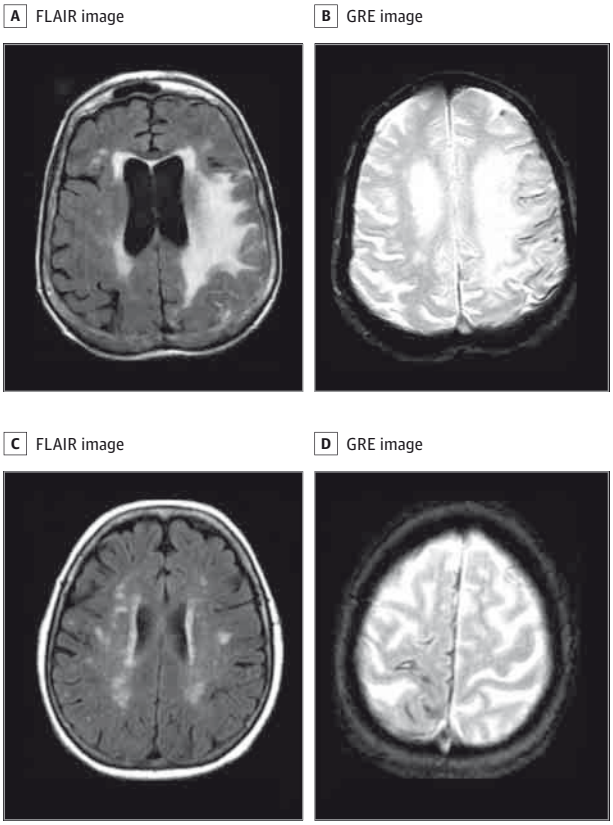
We retrospectively reviewed clinical medical records of all patients seen at the Massachusetts General Hospital (MGH) between October 1, 1995, and May 31, 2013, who were pathologically diagnosed as having CAA-ri. The dates of our analysis were September 1, 2012, to August 31, 2015. Individuals were identified from a prospective cohort of patients diagnosed as having CAA and from review of the database maintained by the MGH neuropathology laboratory, as described elsewhere.[1,2] Of 22 originally identified patients (12 of whom had been previously reported[2]), we excluded 7 for not having full MRI scans (including both FLAIR and gradient-echo [GRE] sequences) before acquisition of the neuropathological sample. Two additional individuals (one previously reported[9]) were obtained from a similar retrospective review of patients seen between January 1, 2009, and December 31, 2011, through The Inflammatory Cerebral Amyloid Angiopathy and Alzheimer's Disease βiomarkers International Network at the University of Milano-Bicocca, Monza, Italy, which left 17 individuals with pathologically confirmed CAA-ri for analysis. We compared these individuals with all patients seen at the MGH over the same period with pathological diagnosis of noninflammatory CAA (definite or probable, with supporting pathological CAA by the Boston criteria[10]) and full MRI scans. The 37 identified control participants were further divided into those with

Table 1. Criteria for the Diagnosis of CAA-ri

Diagnosis	Criteria
Probable CAA-ri	1. Age ≥40 y 2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH 3. MRI shows unifocal or multifocal WMH lesions (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8] 5. Absence of neoplastic, infectious, or other cause
Possible CAA-ri	1. Age ≥40 y 2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH 3. MRI shows WMH lesions that extend to the immediately subcortical white matter 4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8] 5. Absence of neoplastic, infectious, or other cause

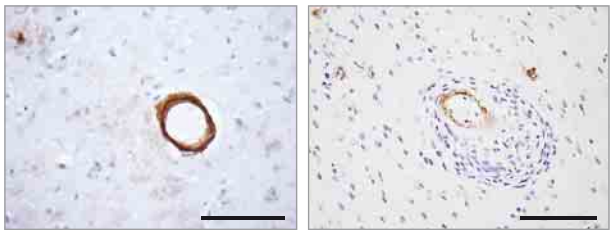
Abbreviations: CAA-ri, cerebral amyloid angiopathy–related inflammation; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

Figure 1. Neuroimaging Features of Probable and Possible Cerebral Amyloid Angiopathy–Related Inflammation (CAA-ri)



Both individuals (a 75-year-old woman in A and B and an 80-year-old woman in C and D) had similar findings (cortical superficial siderosis[8]) on gradient-echo (GRE) images. The fluid-attenuated inversion recovery (FLAIR) image in A meets the criteria for probable CAA-ri, and the FLAIR image in C meets the criteria for possible CAA-ri. Neuropathological data were positive for CAA-ri in A and B and were negative for CAA-ri in C and D.

Figure 2. Characteristic Pathological Findings of Sporadic Cerebral Amyloid Angiopathy (CAA) and a CAA-Related Inflammation Case From Brain Biopsy Samples Stained With Anti–β-Amyloid Antibodies (Brown)



A, Dense amyloid deposition spans the entire vessel wall in a small cortical vessel without any associated inflammatory cells within the vessel wall or in the perivascular space. B, Inflammatory perivascular cell infiltrate surrounds an amyloid-laden small vessel. Scale bar = 100 µm.

past ICH (n = 21) and those with cerebral microbleeds (CMB) only and no history of ICH (n = 16). Fourteen of 21 individuals (67%) with past ICH were diagnosed based on hematoma evacuation, and the diagnoses in the others were based on autopsy.

Demographic and clinical data, including age, sex, and initial clinical presentation, were obtained by clinical medical record review. All aspects of the study were approved by the institutional review boards of the 2 referral centers. All patients analyzed in this study provided written informed consent or were included under a waiver of consent for data review as part of protocols approved by the Partners Human Research Committee (Boston, Massachusetts) and the San Gerardo Hospital Ethical Committee (Monza, Italy).

MRI Acquisition and Analysis

All participants underwent brain MRI on a 1.5-T imaging system (Signa; GE Medical Systems) using the previously reported parameters.[11,12] All images were evaluated in random order for ICH, CMB,[13] and superficial siderosis (on GRE sequences) and WMH pattern (on FLAIR) by a trained neurologist (E.A.) without knowledge of patients' clinical or pathological data. A subset of 12 randomly selected patient scans (6 with CAA-ri, 2 with noninflammatory CAA with lobar ICH, and 4 with noninflammatory CAA with no ICH) was independently evaluated by a second trained neurologist (J.N.) and compared with the findings of the original reader to assess interrater reliability.

Pathological Data

Surgical specimens were processed per usual clinical pathology methods with formalin fixation, standard paraffin embedding, hematoxylin-eosin staining, immunohistochemistry directed against β-amyloid, and Congo red staining. Autopsy brain specimens were formalin fixed for 10 to 14 days before dissection. Histological sections corresponding to the recommendations of the Consortium to Establish a Registry for Alzheimer's Disease[14] and the National Institute on Aging-Alzheimer's Association scheme for the diagnosis of Alzheimer disease[15] were examined, along with an additional series of cortical blocks covering orbitofrontal cortex and cingulate gyrus, as well as deep gray matter, brainstem. and cerebellum. These blocks were stained with Luxol fast blue–hematoxylin-eosin, in addition to immunohistochemistry for β-amyloid (anti-human β-amyloid clone 6F/3D, catalog number M0872; Dako) and silver staining (modified Bielschowsky method). Staining was performed on an autostainer (Bond 3; Leica).

Diagnostic criteria for CAA-ri were evidence of 1 or more CAA-positive vessels with lymphocytes in the vessel wall or perivascular histiocytes (not associated with hemosiderin) (**Figure 2**). Macrophages or bland lymphocytic perivascular cuffs associated with CAA-affected vessels were not considered diagnostic for CAA-ri because they are sometimes found in sporadic CAA.

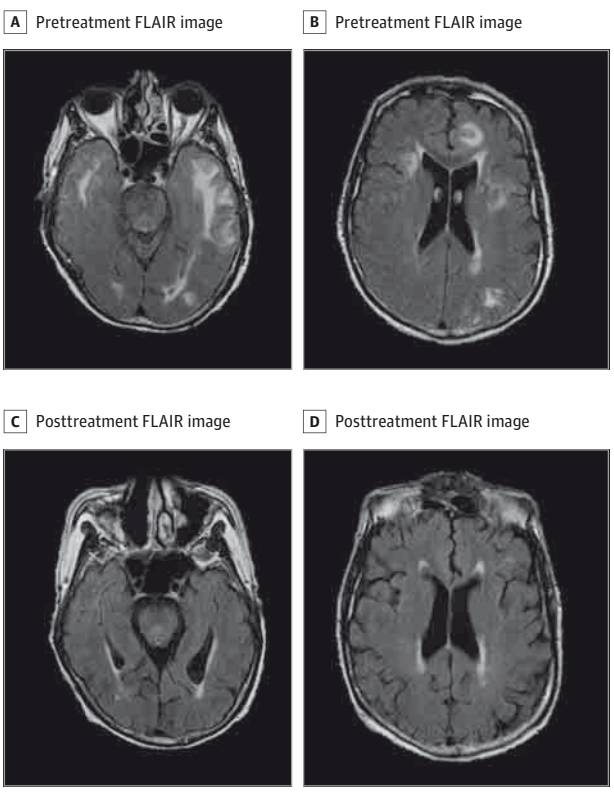
All slides were reviewed initially by diagnostic neuropathologists. A representative subset of 18 slides (4 diagnosed as CAA-ri and 14 diagnosed as noninflammatory CAA) was independently reviewed by a second trained rater (A.C.) without knowledge of patients' clinical, imaging, or previous pathological rating. Interrater reliability for the diagnostic classification of CAA-ri was excellent (κ = 0.87).

Table 2. Characteristics of Participants With CAA-ri and Noninflammatory CAA Control Group Members

Variable	CAA-ri (n = 17)	Noninflammatory CAA Control Group		P Value
		CAA With Lobar ICH (n = 21)	CAA With No ICH (n = 16)	
Age, mean (SD), y	68 (8)	69 (10)	76 (10)	.05
Female sex, No. (%)	8 (47)	13 (62)	9 (56)	.66
Cerebral microbleed, median (IQR), No.	7 (1-27.5)	3 (0-26.5)	10.5 (3.3-35.3)	.74
Cortical superficial siderosis, No. (%)	4 (24)	8 (38)	4 (25)	.55

Abbreviations: CAA-ri, cerebral amyloid angiopathy–related inflammation; ICH, intracerebral hemorrhage; IQR, interquartile range.

Figure 3. Pretreatment and Posttreatment Fluid-Attenuated Inversion Recovery (FLAIR) Images in a 75-Year-Old Man



A and B, Shown are hyperintensities involving the temporal lobes bilaterally (A) and the left frontal lobe and parieto-occipital lobe (B). A brain biopsy specimen demonstrated cerebral amyloid angiopathy (CAA), without evidence of inflammation. The patient began a high-dose, 5-day course of intravenous corticosteroids. C and D, One and a half months after the initial presentation, significant resolution of edema and white matter hyperintensities is seen.

Results

We prespecified diagnostic criteria for CAA-ri based on typical clinical features and the presence of extensive asymmetric WMHs (probable CAA-ri) (Table 1) or extensive WMHs not required to be asymmetric (possible CAA-ri). These criteria were applied without knowledge of pathological diagnosis to 17 patients pathologically diagnosed as having CAA-ri, 21 patients pathologically diagnosed as having noninflammatory CAA with lobar ICH, and 16 patients pathologically diagnosed as having noninflammatory CAA without lobar ICH (**Table 2**). Interrater reliability for the MRI features of probable and possible CAA-ri (Table 1) were high (κ = 0.81 for both).

In the CAA-ri group, 14 of 17 (82%) met the criteria for both probable and possible CAA-ri. In the control group having noninflammatory CAA with lobar ICH, 1 of 21 (5%) met the criteria for possible CAA-ri, and none met the criteria for probable CAA-ri. In the control group having noninflammatory CAA with no ICH, 11 of 16 (69%) met the criteria for possible CAA-ri, and 1 of 16 (6%) met the criteria for probable CAA-ri. These findings yielded a sensitivity and specificity of 82% and of 97%, respectively, for the probable criteria and a sensitivity and specificity of 82% and 68%, respectively, for the possible criteria.

We performed exploratory post hoc analysis of available diffusion-weighted imaging (DWI) and contrast-enhanced images. Small hyperintense DWI lesions were found in 1 of 13 (8%) in the CAA-ri group, in 6 of 18 (33%) in the group with noninflammatory CAA with lobar ICH, and in 3 of 16 (19%) in the group with noninflammatory CAA with no ICH (P = .22). Gadolinium enhancement was found in 3 of 13 (23%) in the CAA-ri group (2 parenchymal and leptomeningeal and 1 leptomeningeal only), in 1 of 11 (9%) in the group with noninflammatory CAA with lobar ICH, and in 1 of 8 (13%) in the group with noninflammatory CAA with no ICH (P = .62).

We reviewed the 3 patients with false-negative CAA-ri who did not meet the criteria for probable or possible CAA-ri. One individual, a 52-year-old woman with new-onset seizures and extensive WMH, did not have any hypointense lesions on GRE indicative of hemorrhage. The second individual was a 69-year-old woman with recurrent focal neurological deficits and multiple CMBs but no WMH on FLAIR. The third individual was a 69-year-old woman with 3 weeks of fluctuating symptoms of headache, visual hallucinations, and decrease in consciousness. Magnetic resonance imaging showed no extensive WMH. During admission, she developed a large ICH.

The 1 control participant who met the criteria for probable CAA-ri was a 75-year-old man with subacute cognitive decline and gait impairment, in addition to asymmetric multiple foci of WMH and numerous CMBs. Although a Congo red-positive biopsy specimen did not show any areas of inflammation but rather areas of white matter gliosis, the patient was nonetheless treated with 6 days of high-dose corticosteroids. He subsequently had clinical and radiographic improvement, with his decreased consciousness and gait returning close to baseline and with marked reduction in asymmetric subcortical WMH foci (**Figure 3**).

Discussion

Although neuropathological examination remains the definitive diagnostic approach to CAA-ri, our data suggest that a reliable diagnosis can be reached from basic clinical and radiographic information alone, with good sensitivity and excellent specificity. Pending further validation studies, the modified probable CAA-ri criteria seem sufficiently specific to be incorporated into clinical practice for identifying patients who can be treated without the requirement of an invasive brain biopsy.

The probable CAA-ri criteria proposed herein appear to offer the best sensitivity and specificity combination. The less restrictive definition for WMH patterns in the possible CAA-ri criteria (Table 1) did not result in better sensitivity but rather lowered the specificity from 97% to 68%. Because extensive WMH per se is common in noninflammatory and inflammatory CAA,[16] the specificity of any proposed criteria depends on defining the particular patterns of WMH that are most characteristic of CAA-ri.

Balancing the risks and benefits of brain biopsy vs empirical high-dose corticosteroid therapy in patients with suspected CAA-ri poses a clinical challenge. Although stereotactic brain biopsy is usually safe, complications may occur, with mortality reported in 0% to 1% of cases and significant morbidity reported in 3% to 5% of cases.[17,18] Short-term, high-dose corticosteroid therapy is generally well tolerated, although acute complications, such as psychosis and hyperglycemia, are common.[19] Corticosteroid therapy may also obscure the diagnosis of certain disorders, such as cerebral lymphoma,[20] offering a second argument against empirical treatment without strong clinical evidence of CAA-ri.

The results of other clinical investigations not incorporated into the present criteria may also have a role in the noninvasive diagnosis of CAA-ri. One finding that supports the diagnosis of CAA-ri is response to immunosuppressive therapy, typically high-dose corticosteroids or cyclophosphamide.[1-3] The present study did not include response to treatment because our goal was to use information only available at the time when choosing between empirical immunosuppression and brain biopsy. Our findings also indicate that we cannot rely on small DWI hyperintense lesions or gadolinium enhancement for the diagnosis. Cerebral amyloid angiopathy–related inflammation can also be suggested by cerebrospinal fluid (CSF) abnormalities, such as mildly elevated protein[2] and the presence of leukocytes. However, these findings appear to be neither sensitive nor specific for the diagnosis. Most intriguingly, a study[21] found elevated CSF anti–β-amyloid autoantibodies during the acute phase of CAA-ri and not in noninflammatory CAA or other non-CAA inflammatory disorders. Although CSF anti–β-amyloid autoantibodies are not yet routinely included in clinical practice, validation of experimental cutoff values for CAA-ri diagnostic confirmation is the subject of current active research by The Inflammatory Cerebral Amyloid Angiopathy and Alzheimer's Disease βiomarkers International Network,[22] highlighting the need for clinical diagnostic methods.[23,24]

Notable strengths of our study are the inclusion of pathological confirmation for all participants and a masked analysis. The main limitations are its retrospective design and the few cases (n = 17), although our total represents the largest reported group of patients with pathologically diagnosed CAA-ri to date. The restriction to cases with pathology samples typically favors patients with atypical or more aggressive clinical presentations, who may be more likely to undergo brain biopsy, raising the possibility that the findings herein may not be fully generalizable to all patients with CAA-ri. We also note that the focal and segmental nature of the inflammatory response[25] can cause the disease to be missed on biopsy. Indeed, the one false-positive individual in the present study demonstrated a clinicoradiological response to treatment consistent with CAA-ri (Figure 3), suggesting that the proposed probable criteria may in fact have detected CAA-ri with 100% specificity in our data set.

Conclusions

The present data support using empirical immunosuppressive therapy (and avoiding brain biopsy) for patients meeting the criteria proposed for probable CAA-ri. A reasonable follow-up approach would be to consider brain biopsy in empirically treated patients who fail to respond to corticosteroid therapy within 3 weeks.[3] Cerebral amyloid angiopathy–related inflammation is the most readily treatment-responsive subtype of CAA, highlighting the importance of reaching this diagnosis in clinical practice in as many affected patients as possible.

ARTICLE INFORMATION

Accepted for Publication: October 29, 2015.

Published Online: December 28, 2015. doi:10.1001/jamaneurol.2015.4078.

Author Affiliations: The J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston (Auriel, Charidimou, Gurol, Ni, Van Etten, Martinez-Ramirez, Boulouis, Pontes-Neto, Shoamanesh, Reijmer, Vashkevich, Ayres, Schwab, Viswanathan, Greenberg); The Inflammatory Cerebral Amyloid Angiopathy and Alzheimer's Disease βiomarkers International Network, University of Milano-Bicocca, Monza, Italy (Auriel, Piazza, DiFrancesco, Greenberg); Milan Center for Neuroscience, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy (Piazza, DiFrancesco); Neuropathology Service, C. S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School, Boston (Frosch); Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada (Shoamanesh).

Author Contributions: Dr Greenberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Auriel, Gurol, Greenberg.
Acquisition, analysis, or interpretation of data: Auriel, Charidimou, Ni, Van Etten, Martinez-Ramirez, Boulouis, Piazza, DiFrancesco, Frosch, Pontes-Neto, Shoamanesh, Reijmer, Vashkevich, Ayres.
Drafting of the manuscript: Auriel, Greenberg.
Critical revision of the manuscript for important intellectual content: Auriel, Charidimou, Gurol, Boulouis, Viswanathan, Greenberg.
Study supervision: Schwab, Viswanathan, Greenberg.

Conflict of Interest Disclosures: Dr Viswanathan reported receiving a research grant from the National Institutes of Health and reported serving on the data safety monitoring board for Roche Pharmaceuticals. Dr Greenberg reported receiving

research grant R01AG26484, as well as other funding, from the National Institutes of Health. No other disclosures were reported.

Funding/Support: This project was supported by grant R01AG26484 from the National Institutes of Health (Dr Greenberg), by competitive research fund 12-1-2002100-2015 from the University of Milano-Bicocca, and by The Inflammatory Cerebral Amyloid Angiopathy and Alzheimer's Disease βiomarkers–Italy Study Group of the Italian Society of Neurology for the Study of Dementia.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy–related inflammation. *Ann Neurol*. 2004;55(2):250-256.

2. Kinnecom C, Lev MH, Wendell L, et al. Course of cerebral amyloid angiopathy–related inflammation. *Neurology*. 2007;68(17):1411-1416.

3. Chung KK, Anderson NE, Hutchinson D, Synek B, Barber PA. Cerebral amyloid angiopathy related inflammation: three case reports and a review. *J Neurol Neurosurg Psychiatry*. 2011;82(1):20-26.

4. Sperling R, Salloway S, Brooks DJ, et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. *Lancet Neurol*. 2012;11(3):241-249.

5. Black RS, Sperling RA, Safirstein B, et al. A single ascending dose study of bapineuzumab in patients with Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2010;24(2):198-203.

6. Werring DJ, Sperling R. Inflammatory cerebral amyloid angiopathy and amyloid-modifying therapies: variations on the same ARIA? *Ann Neurol*. 2013;73(4):439-441.

7. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010;74(17):1346-1350.

8. Charidimou A, Linn J, Vernooij MW, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain*. 2015;138(pt 8):2126-2139.

9. DiFrancesco JC, Brioschi M, Brighina L, et al. Anti-Aβ autoantibodies in the CSF of a patient with CAA-related inflammation: a case report. *Neurology*. 2011;76(9):842-844.

10. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology*. 2001;56(4):537-539.

11. Gurol ME, Irizarry MC, Smith EE, et al. Plasma β-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. *Neurology*. 2006;66(1):23-29.

12. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. *Stroke*. 2004;35(6):1415-1420.

13. Greenberg SM, Vernooij MW, Cordonnier C, et al; Microbleed Study Group. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8(2):165-174.

14. Fillenbaum GG, van Belle G, Morris JC, et al. Consortium to Establish a Registry for Alzheimer's Disease (CERAD): the first twenty years. *Alzheimers Dement*. 2008;4(2):96-109.

15. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement*. 2012;8(1):1-13.

16. Gurol ME, Viswanathan A, Gidicsin C, et al. Cerebral amyloid angiopathy burden associated with leukoaraiosis: a positron emission tomography/magnetic resonance imaging study. *Ann Neurol*. 2013;73(4):529-536.

17. Kreth FW, Muacevic A, Medele R, Bise K, Meyer T, Reulen HJ. The risk of haemorrhage after image guided stereotactic biopsy of intra-axial brain tumours: a prospective study. *Acta Neurochir (Wien)*. 2001;143(6):539-545.

18. Shakal AA, Mokbel EA. Hemorrhage after stereotactic biopsy from intra-axial brain lesions: incidence and avoidance. *J Neurol Surg A Cent Eur Neurosurg*. 2014;75(3):177-182.

19. Ross DA, Cetas JS. Steroid psychosis: a review for neurosurgeons. *J Neurooncol*. 2012;109(3):439-447.

20. Geppert M, Ostertag CB, Seitz G, Kiessling M. Glucocorticoid therapy obscures the diagnosis of cerebral lymphoma. *Acta Neuropathol*. 1990;80(6):629-634.

21. Piazza F, Greenberg SM, Savoiardo M, et al. Anti-amyloid β autoantibodies in cerebral amyloid angiopathy–related inflammation: implications for amyloid-modifying therapies. *Ann Neurol*. 2013;73(4):449-458.

22. Piazza F. Inflammatory CAA and AD and Biomarkers International Network. https://sites.google.com/site/icabinternationalnetwork/home. Accessed November 13, 2015.

23. Boncoraglio GB, Piazza F, Savoiardo M, et al. Prodromal Alzheimer's disease presenting as cerebral amyloid angiopathy–related inflammation with spontaneous amyloid-related imaging abnormalities and high cerebrospinal fluid anti-Aβ autoantibodies. *J Alzheimers Dis*. 2015;45(2):363-367.

24. DiFrancesco JC, Touat M, Caulo M, et al. Recurrence of cerebral amyloid angiopathy–related inflammation: a report of two cases from the *i*CAβ International Network. *J Alzheimers Dis*. 2015;46(4):1071-1077.

25. Scolding NJ, Joseph F, Kirby PA, et al. Aβ-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain*. 2005;128(pt 3):500-515.