REVIEW ARTICLE

Cerebral Amyloid Angiopathy

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SUMMARY

Cerebral amyloid angiopathy is a major cause of hemorrhagic stroke, a frequent contributor to age-related cognitive impairment, and a key component in adverse responses to beta-amyloid (Aβ) immunotherapy. Defined by pathological deposition of Aβ in the small blood vessels of the brain, cerebral amyloid angiopathy is most often diagnosed on the basis of magnetic resonance imaging studies showing multiple hemorrhages or leptomeningeal blood products within or overlying the cerebral cortex. The disorder typically manifests as hemorrhagic stroke or as a contributing factor to cognitive decline and, less commonly, with transient focal neurologic symptoms or a cerebral inflammatory autoimmune syndrome. The high risk of recurrent hemorrhagic strokes associated with cerebral amyloid angiopathy poses a particular challenge in patients with indications for antithrombotic therapy and dictates a carefully individualized weighing of risks and benefits. Ongoing research is focused on tools to aid in risk prediction, early diagnostic markers, and identification of key pathogenic steps as targets for disease-modifying therapies.

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CME

Cerebral amyloid angiopathy is an age-associated cause of cerebral hemorrhages, cognitive decline, and transient neurologic episodes that can mimic transient ischemic attacks. The disorder has hidden in plain sight through much of its history. In its common sporadic form, it is defined by deposition of the beta-amyloid (Aβ) peptide in walls of the small blood vessels of the brain and has a close relationship with the Aβ-containing plaques of Alzheimer's disease. First reported as a postmortem observation by the German investigator Gustav Oppenheim in 1909[1] (just 2 years after Alois Alzheimer's published report of the disease that would eventually be named Alzheimer's disease), cerebral amyloid angiopathy was not linked to clinical events such as intracerebral hemorrhage until the second half of the 20th century. Subsequent progress has led to cerebral amyloid angiopathy being diagnosable in living patients. Along with its role in causing intracerebral hemorrhage and in contributing to age-related cognitive decline, cerebral amyloid angiopathy affects clinical decisions about the use of anticoagulation therapy in stroke treatment and prevention and the use of anti-Aβ immunotherapies for Alzheimer's disease.

PATHOGENESIS AND EPIDEMIOLOGY

The Aβ fibril deposits that characterize cerebral amyloid angiopathy differ from those in Alzheimer's disease in that they are primarily localized to cerebral blood-vessel walls rather than brain tissue and are characterized by a predominance of the shorter Aβ40 isoform rather than the longer Aβ42 isoform.[2] The pathological changes range from trace Aβ deposits surrounding arteriolar smooth-

muscle cells (mild cerebral amyloid angiopathy, Fig. 1A) to full replacement of the arteriolar media (moderate cerebral amyloid angiopathy, Fig. 1A) and, ultimately, to fragmentation of the vessel wall (severe cerebral amyloid angiopathy, Fig. 1B).[3] Amyloid is predominantly deposited in leptomeningeal and cortical arterioles, but it may appear in cerebral capillaries, otherwise sparing cerebral veins, venules, larger arteries, and deep penetrating arterioles in the basal ganglia, thalamus, and brain stem. Deposits are absent in vessels outside the central nervous system. Intracerebral hemorrhage occurs at the severe pathological stage[3] and is likely to be the result of vascular remodeling that leads to replacement of Aβ-laden vessel-wall segments with fibrin and other plasma components, blood–brain barrier leakage, and accumulation of activated astrocytes and perivascular microglia or macrophages.[4]

Although the pathological changes that characterize cerebral amyloid angiopathy and Alzheimer's disease can appear independently, they co-occur more frequently than by chance. On the basis of pooled data from postmortem neuropathological studies, the estimated prevalence of moderate-to-severe cerebral amyloid angiopathy is 23.0% in the general population and 47.5% among patients with Alzheimer's disease.[5] The tendency for the two diseases to overlap is probably related to shared pathophysiological mechanisms of Aβ deposition, as well as partially shared predisposing risk factors, such as the presence and dose of the ε4 allele of *APOE*, the gene encoding apolipoprotein E.[2] The prevalence of moderate-to-severe cerebral amyloid angiopathy substantially exceeds the prevalence of hemorrhagic brain lesions related to cerebral amyloid angiopathy such as microbleeds (asymptomatic cerebral hemorrhages of <10 mm in diameter as detected on magnetic resonance imaging [MRI]), which have an estimated prevalence of 7.1% in the general population and 21.8% among persons with Alzheimer's disease.[5] The fact that the

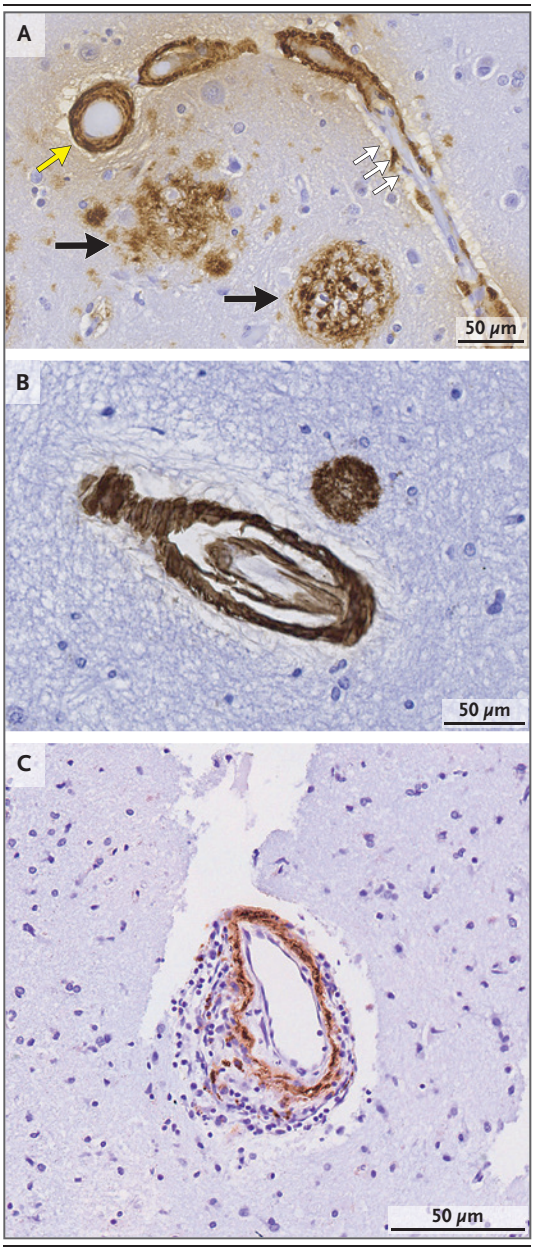

Figure 1. Neuropathological Features of Cerebral Amyloid Angiopathy.

The vessels in Panel A show both mild cerebral amyloid angiopathy, characterized by beta-amyloid (Aβ) deposits (white arrows) alternating with unaffected vessel segments, and moderate cerebral amyloid angiopathy, characterized by complete replacement of the vessel wall with Aβ (yellow arrow). Segment-to-segment variation in the severity of cerebral amyloid angiopathy within a brain is typical. The section also shows Aβ-containing senile plaques (black arrows). Panel B shows severe cerebral amyloid angiopathy, with concentric splitting of the Aβ-laden vessel wall creating a vessel-within-vessel appearance. The vessel segment in Panel C shows inflammation related to cerebral amyloid angiopathy, with an infiltration of mononuclear inflammatory cells surrounding an Aβ-positive segment. Anti-Aβ immunohistochemical staining was used for the sections in all three panels, with hematoxylin counterstaining. These neuropathological images are courtesy of Drs. Susanne van Veluw and Francesco Bax.

prevalence of cerebral amyloid angiopathy is higher than the prevalence of hemorrhagic lesions related to cerebral amyloid angiopathy supports the idea that brain hemorrhages develop in only a subgroup of persons with advanced cerebral amyloid angiopathy.

Much of our understanding of how cerebral amyloid angiopathy progresses from presymptomatic to symptomatic stages has come from longitudinal analysis of rare autosomal dominant, fully penetrant hereditary forms of cerebral amyloid angiopathy, such as that caused by the Dutch-type amyloid precursor protein (APP) mutation.[6] Studies in APP mutation carriers suggest that the earliest vascular Aβ deposits occur approximately 30 to 40 years before the first intracerebral hemorrhage, a finding inferred from an observed reduction of Aβ in cerebrospinal fluid, a correlate of increased brain deposition, during that period. The next detectable change, occurring 20 to 30 years before the first intracerebral hemorrhage, is impaired cerebrovascular function, measured by functional MRI as reduced reactivity to physiologic stimulation, which probably reflects a loss of smooth vessel cells from arteriolar segments affected by cerebral amyloid angiopathy. The first evidence of brain-tissue injury, detected by sensitive measures of structural integrity such as diffusion-tensor MRI, appear 10 to 15 years before the first intracerebral hemorrhage. Finally, cerebral amyloid angiopathy–associated hemorrhagic lesions, a category that includes lobar intracerebral hemorrhage (i.e., a lesion situated within a lobe of the brain rather than in deep structures), microbleeds, and leptomeningeal foci of blood products (cortical superficial siderosis), appear as the culmination of this multidecade process.

Although this timeline is derived largely from studies involving APP mutation carriers, there is ancillary evidence of a similar decades-long timeline for the rare form of iatrogenic cerebral amyloid angiopathy appearing in persons who in early life had neurosurgical exposure to human cadaveric grafts containing Aβ. The mean interval between the presumed exposure and the first cerebral amyloid angiopathy–related symptomatic presentation in such persons is 36 years.[7] The timeline for cerebral amyloid angiopathy appears to exceed the approximately 20-year interval between the first appearance of Aβ biomarkers and the diagnosis of Alzheimer's disease,[8] which suggests that cerebral amyloid angiopathy requires roughly one to two decades longer to progress from the first deposits of Aβ to symptomatic disease.

CLINICAL MANIFESTATIONS

Cerebral amyloid angiopathy can become apparent acutely as a symptomatic hemorrhagic stroke or insidiously as a contributor to progressive cognitive impairment. Intracerebral hemorrhage related to cerebral amyloid angiopathy, reflecting the locus of cerebral amyloid angiopathy, occurs predominantly in the superficial cortex, adjacent subarachnoid space, and subcortical white matter[9] (Fig. 2A). Hemorrhages can also involve the superficial cerebellar cortex[10] but spare deep gray-matter structures such as the putamen, thalamus, and brain stem, which are the regions most affected by arteriolosclerosis-related intracerebral hemorrhage. Symptoms of intracerebral hemorrhage related to cerebral amyloid angiopathy, like those of other hemorrhagic strokes, vary according to the location and volume of disrupted brain tissue.

In contrast to the acute stroke syndromes associated with intracerebral hemorrhage, cognitive decline associated with cerebral amyloid angiopathy evolves gradually over months and years without symptomatic stroke. The Rush Memory and Aging study and the Religious Orders study, which are longitudinal clinical–pathological studies, have shown that postmortem findings of moderate-to-severe cerebral amyloid angiopathy, as compared with mild or no cerebral amyloid angiopathy, are independently associated with worse cognitive performance and a faster rate of cognitive decline before death in an analysis adjusted for age, sex, educational level, and concomitant age-related neuropathological disease, including Alzheimer's disease, arteriolosclerosis, atherosclerosis, and other neurodegenerative processes.[11] This analysis estimated that when moderate-to-severe cerebral amyloid angiopathy disease is present (it was found in more than one third of autopsied brains in the study sample), it accounts for approximately 16% of a person's cognitive loss.

Cerebral amyloid angiopathy probably affects cognition through several types of brain lesions,

including MRI-detected white-matter hyperintensities[12] and cerebral microinfarcts.[13] Like other vascular contributions to cognitive impairment and dementia, cerebral amyloid angiopathy has the greatest effect on processing speed and executive function.[14,15] The clinical course of gradually worsening performance across multiple cognitive domains, including episodic memory, can be indistinguishable from the effects of Alzheimer's disease.

A third, increasingly recognized clinical manifestation of cerebral amyloid angiopathy is multiple brief spells (typically lasting less than 30 minutes) of focal motor weakness, sensory loss, tingling, dysarthria, or aphasia. Unlike the symptoms of transient ischemic attacks, the symptoms in these spells often spread along contiguous body parts over the course of minutes.[16] These episodes frequently recur in clusters over a period of days or weeks in a stereotyped manner, with only slight variations in the timing and extent of spread. Computed tomography (CT) or MRI in patients with transient focal neurologic episodes due to cerebral amyloid angiopathy frequently discloses recent convexity subarachnoid hemorrhage or cortical superficial siderosis adjacent to cortical re-

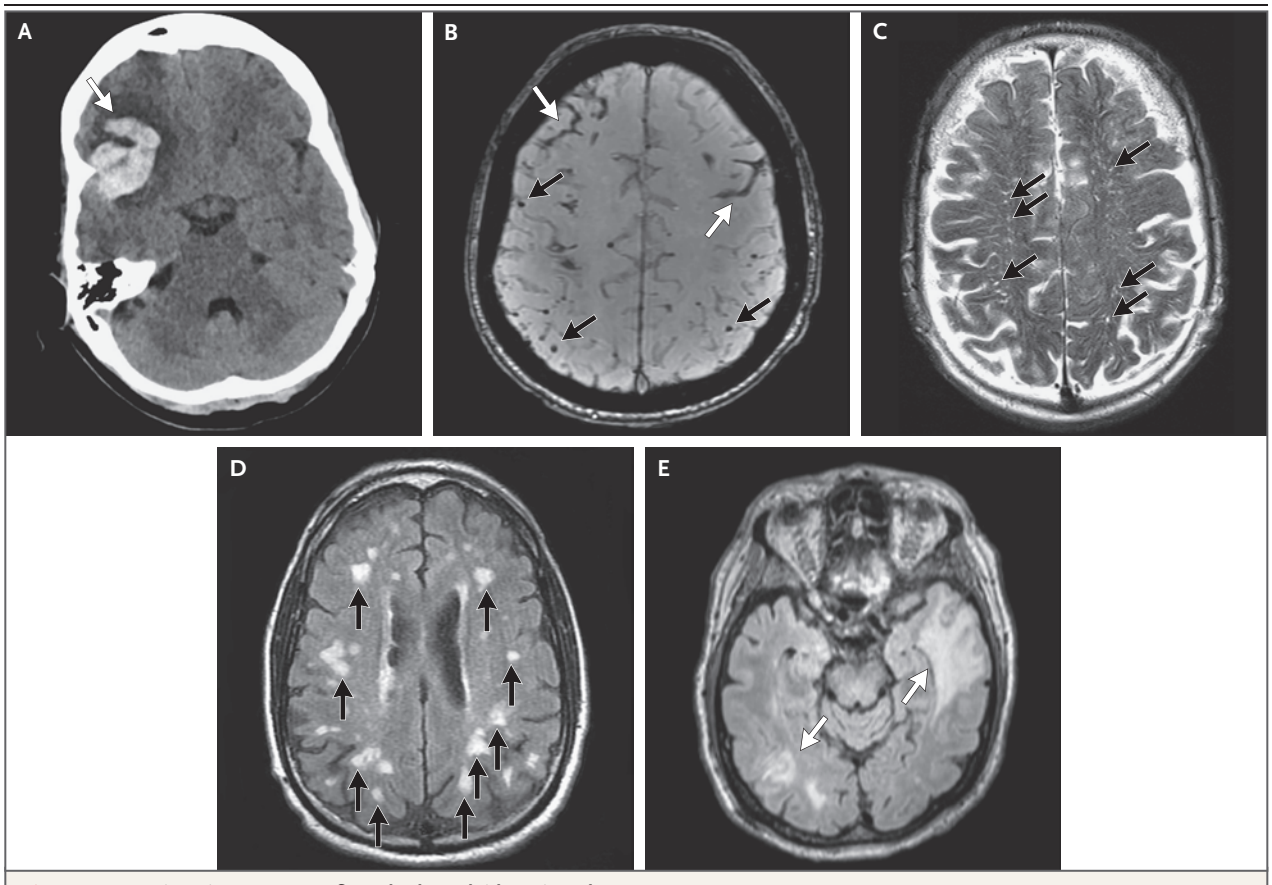

Figure 2. Neuroimaging Features of Cerebral Amyloid Angiopathy.

The computed tomographic scan in Panel A shows an acute right frontal lobar intracerebral hemorrhage, with subarachnoid extension and a fingerlike projection (arrow), features that are characteristic of cerebral amyloid angiopathy. In Panel B, magnetic resonance imaging with T2*-weighted images shows two foci of cortical superficial siderosis (white arrows) and multiple lobar cerebral microbleeds (black arrows). Panels C and D show the two types of nonhemorrhagic white-matter lesions incorporated into the Boston criteria for the diagnosis of cerebral amyloid angiopathy: severe (>20 in a hemisphere) visible perivascular spaces in the centrum semiovale seen on T2-weighted images (Panel C, arrows) and a multispot pattern of white-matter hyperintensities (>10 small, circular or ovoid lesions in the subcortical white matter of both hemispheres) on fluid-attenuated inversion recovery (FLAIR) images (Panel D, arrows). Panel E shows two FLAIR-hyperintense lesions in juxtacortical left frontal and right temporo-occipital white matter (arrows), which are characteristic of inflammation related to cerebral amyloid angiopathy, in a patient with a biopsy-confirmed diagnosis of this disorder.

gions associated with the symptoms. The finding of localized blood products and the spread of symptoms, two features that distinguish cerebral amyloid angiopathy–associated transient spells from typical transient ischemic attacks, are consistent with an underlying mechanism of cortical spreading depolarization, the same process that is thought to cause migraine auras.[16]

A fourth clinical manifestation, cerebral amyloid angiopathy–related inflammation, is discussed separately below because of its distinct clinical features, treatment, and implications for understanding amyloid-related imaging abnormalities (ARIA) associated with anti-Aβ immunotherapy for Alzheimer's disease.

DIAGNOSIS

Hemorrhagic stroke, progressive cognitive decline, or transient focal neurologic episodes due to cerebral amyloid angiopathy may occur independently or in combination. Brain imaging in these situations often allows a diagnosis of cerebral amyloid angiopathy without the need to obtain brain tissue for pathological examination, either by hematoma appearance or most often by detection of multiple hemorrhages in characteristic locations. CT studies in patients with lobar intracerebral hemorrhage related to cerebral amyloid angiopathy tend to show blood in the subarachnoid space and fingerlike projections of the hematoma (Fig. 2A), findings that form the basis of the Edinburgh diagnostic criteria for cerebral amyloid angiopathy.[9] In the study defining these criteria, the presence of both subarachnoid blood and fingerlike projections helped to rule in cerebral amyloid angiopathy (specificity, approximately 87%), and the absence of both findings helped to rule out cerebral amyloid angiopathy (sensitivity, 81%). The sensitivity of the Edinburgh criteria appears to be lower for intracerebral hemorrhages that are smaller than 15 ml.[17]

The Boston criteria for cerebral amyloid angiopathy (Table 1) are based on combinations of characteristic MRI findings, including lobar intracerebral hemorrhage, lobar microbleeds, and cortical superficial siderosis (Fig. 2B). These imaging findings are accurately detected by T2*-weighted MRI sequences such as gradient-echo and susceptibility-weighted imaging. The presence of at least two lobar hemorrhagic lesions (intracerebral hemorrhage, microbleeds, or foci of cortical superficial siderosis) without hemorrhages in deep-brain regions or other causes of hemorrhage meets the Boston criteria for probable cerebral amyloid angiopathy (Table 1). The most recent revision of the Boston criteria also allows the diagnosis of probable cerebral amyloid angiopathy in the presence of one lobar hemorrhagic lesion plus one nonhemorrhagic MRI marker associated with cerebral amyloid angiopathy: severe visible perivascular spaces in the centrum semiovale (Fig. 2C) or white-matter hyperintensities in a multispot pattern (Fig. 2D).

In an MRI–pathological validation analysis, the imaging diagnosis of probable cerebral amyloid angiopathy according to the Boston criteria corresponded to pathological evidence of moderate-to-severe cerebral amyloid angiopathy in the brain at autopsy with approximately 74.5% sensitivity and 95.0% specificity,[18] with the greatest sensitivity (90.2%) for patients presenting with lobar intracerebral hemorrhage and lower sensitivity (55.1%) for those with clinical presentations such as cognitive decline in the absence of intracerebral hemorrhage. The higher diagnostic sensitivity with clinical presentations that include intracerebral hemorrhage supports the idea that cerebral amyloid angiopathy can be advanced enough to contribute to cognitive impairment without necessarily triggering even the one hemorrhagic lesion that the Boston criteria require for the diagnosis of probable cerebral amyloid angiopathy (Table 1). The category of probable cerebral amyloid angiopathy with supporting pathological findings applies when cerebral amyloid angiopathy–positive tissue is available from a brain biopsy or from tissue obtained during hematoma evacuation. The diagnosis of definite cerebral amyloid angiopathy under these criteria requires evidence of severe cerebral amyloid angiopathy in the brain at autopsy.

Positron-emission tomography with amyloid-selective tracers has been shown to detect cerebral amyloid angiopathy[19] but does not readily distinguish between Alzheimer's disease and cerebral amyloid angiopathy. Cerebrospinal fluid from patients with cerebral amyloid angiopathy shows reductions in both the Aβ42 isoform and the Aβ40 isoform,[20] findings that can help con-

firm the diagnosis and may help differentiate cerebral amyloid angiopathy from Alzheimer's disease (which does not cause a reduced level of the Aβ40 isoform in cerebrospinal fluid).

TREATMENT AND PROGNOSIS

Other than its characteristic lobar location, acute intracerebral hemorrhage related to cerebral amyloid angiopathy does not systematically differ from other forms of acute intracerebral hemorrhage with respect to clinical appearance, course, or response to treatment. The risk of hematoma expansion, for example, did not differ significantly between 202 patients with lobar intracerebral hemorrhage that met the Edinburgh or Boston criteria for cerebral amyloid angiopathy and 1637 patients with nonlobar intracerebral hemorrhage who were enrolled in the Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage trial.[21] With regard to the safety of hematoma evacuation, a systematic review of 352 suspected cases of intracerebral hemorrhage related to cerebral amyloid angiopathy in which patients underwent surgical intervention (primarily open craniotomy) showed a low incidence of intraoperative hemorrhage (0.6%, 2 of 352 patients), and the estimated incidence of postoperative hemorrhage was similar to that for other types of intracerebral hemorrhage.[22] Current guidelines regarding the diagnosis and treatment of acute intracerebral hemorrhage, as well as the prognosis, do not draw distinctions between intracerebral hemorrhages that are related and those that are unrelated to cerebral amyloid angiopathy.[23,24]

Nevertheless, the recurrence rate is higher for hemorrhage associated with cerebral amyloid angiopathy (typically at other lobar locations in the brain) than for other forms of intracerebral hemorrhage. A meta-analysis of data from 1306 patients with intracerebral hemorrhage showed that the annual rate of recurrence was 7.4% (95% confidence interval [CI], 3.2 to 12.6) for intracerebral hemorrhage that was related to cerebral amyloid angiopathy as compared with 1.1% (95% CI, 0.5 to 1.7) for intracerebral hemorrhage that was unrelated to cerebral amyloid angiopathy,[25] which places cerebral amyloid angiopathy–related intracerebral hemorrhage among the most frequently recurrent stroke subtypes. Recurrence rates have been highest among patients with cortical superficial siderosis (particularly multifocal or disseminated siderosis) or multiple previous intracerebral hemorrhages.[25-27] Conversely, patients in whom cerebral amyloid angiopathy is diagnosed on the basis of multiple lobar microbleeds alone, in the absence of larger intracerebral hemorrhages and cortical superficial siderosis, appear to be at relatively low risk for future intracerebral hemorrhage, with an estimated risk of 6% over a period of 5 years in a single-center study involving 80 probable cerebral amyloid angiopathy cases.[28] Other factors reported to be associated with an increased risk of recurrent intracerebral hemorrhage related to cerebral amyloid angiopathy are higher blood pressures[29] and an *APOE* genotype containing the ε4 or ε2 allele.[30] Although the *APOE* genotype affects the risk of recurrent hemorrhage, it is typically not assayed in the care of patients with cerebral amyloid angiopathy.

The risk of a future intracerebral hemorrhage is an important consideration in decisions about antithrombotic therapy for patients with cerebral amyloid angiopathy. For the relatively common situation of nonvalvular atrial fibrillation

Table 1. Boston Criteria, Version 2.0, for Probable Cerebral Amyloid Angiopathy.*

Age ≥50 years
Clinical presentation with spontaneous intracerebral hemorrhage, cognitive decline, or transient focal neurologic symptoms
One of the following: Two or more of the following lobar hemorrhagic lesions on T2*-weighted MRI: intracerebral hemorrhages, cerebral microbleeds, foci of cortical superficial siderosis, or convexity subarachnoid hemorrhage One of the above lobar hemorrhagic lesions plus either of the following nonhemorrhagic white-matter features: severe perivascular spaces in the centrum semiovale or white-matter hyperintensities in a multispot pattern
Absence of spontaneous hemorrhagic lesions on T2*-weighted MRI in deep-brain regions atypical of cerebral amyloid angiopathy: basal ganglia, thalamus, and brain stem
Absence of other direct causes of intracranial hemorrhage: severe head trauma, hemorrhagic transformation of ischemic strokes, arteriovenous malformation, hemorrhagic tumor, central nervous system vasculitis, and aneurysmal subarachnoid hemorrhage

* The Boston criteria, version 2.0, were derived from a cohort of 159 patients with intracerebral hemorrhage, cognitive impairment, or transient focal neurologic episodes who underwent MRI and brain-tissue biopsy for histopathological evaluation, with validation in two independent cohorts of 59 and 123 patients.[18] Information in this table is adapted from Charidimou et al.[18]

KEY POINTS

CEREBRAL AMYLOID ANGIOPATHY

- Cerebral amyloid angiopathy, the deposition of beta-amyloid peptide in small blood vessels of the brain, is a common age-associated disease that, when advanced, can cause vessel breakdown and bleeding.
- The major clinical manifestations of cerebral amyloid angiopathy are hemorrhagic strokes that frequently recur and smaller brain injuries that contribute to progressive cognitive decline.
- Cerebral amyloid angiopathy can be diagnosed with high specificity on the basis of magnetic resonance imaging showing multiple bleeds or microbleeds confined to the cortex or leptomeninges, as well as other, nonhemorrhagic lesions in the white matter.
- Decisions regarding antithrombotic treatment for patients with both cerebral amyloid angiopathy and a defined indication for anticoagulation require an individualized balancing of risks and benefits, which includes consideration of the patient's risk of future hemorrhagic strokes.
- Cerebral amyloid angiopathy can trigger a cerebral autoimmune inflammatory syndrome, a condition mimicking the amyloid-related imaging abnormalities identified as the major adverse effect of Alzheimer's disease immunotherapy.
- The priorities for improving prevention of cerebral amyloid angiopathy–related hemorrhage are the development of methods for early detection and candidate treatments for blocking the cascade of pathogenic steps.

in patients with probable cerebral amyloid angiopathy, multiple completed and ongoing randomized clinical trials have not provided clarity about whether to provide anticoagulation therapy.[31,32] Clinicians are therefore advised to weigh the predictors of cardioembolic stroke related to nonvalvular atrial fibrillation[33] against the predictors of intracerebral hemorrhage related to cerebral amyloid angiopathy (listed above) on an individual basis. After consideration of the balance between these factors along with the poor outcomes among patients who have an intracerebral hemorrhage during anticoagulation therapy,[34] the decision might be to administer a direct-acting oral anticoagulant, perform percutaneous left atrial appendage occlusion,[35] or administer antiplatelet monotherapy. For example, my approach to a patient with cerebral amyloid angiopathy who has atrial fibrillation–related stroke and microbleeds but no intracerebral hemorrhage or cortical superficial siderosis might be to consider using a direct oral anticoagulant as a preventive agent, whereas for a patient with cerebral amyloid angiopathy, low-risk atrial fibrillation, and multiple previous intracerebral hemorrhages, I might offer enrollment in a clinical trial or alternatives to anticoagulation, such as left atrial appendage occlusion or antiplatelet monotherapy, which did not appear to substantially increase the risk of recurrent intracerebral hemorrhage in a randomized trial.[36] The vitamin K antagonist warfarin is typically avoided in patients with cerebral amyloid angiopathy in situations in which direct oral anticoagulants are effective because of the higher risk of intracerebral hemorrhage with warfarin.[37]

Blood pressure control (target pressure, <130/80 mm Hg) is recommended for secondary prevention of intracerebral hemorrhage,[23,24] with data suggesting that the benefits also apply to cerebral amyloid angiopathy.[29,38] On the basis of epidemiologic data, avoidance of heavy alcohol use is reasonable for patients who have had an intracerebral hemorrhage.[39] Evidence is equivocal on whether other medication classes, such as statins[40] or selective serotonin-reuptake inhibitors,[41] increase the risk of recurrent intracerebral hemorrhage; an individualized approach in which benefits for defined indications are balanced against risks that have not yet been convincingly demonstrated may therefore be warranted. Although healthy lifestyle and dietary choices are reasonable for all types of cerebrovascular disease, evidence that clearly links lifestyle or dietary factors to cerebral amyloid angiopathy is currently lacking.

CEREBRAL AMYLOID ANGIOPATHY–RELATED INFLAMMATION AND AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA)

The syndrome of inflammation related to cerebral amyloid angiopathy appears to represent an autoimmune response directed to the cerebro-

vascular Aβ deposits (Fig. 1C)[42,43]; the response may be driven by spontaneous generation of anti-Aβ autoantibodies.[44] Characteristic symptoms of this distinctive form of cerebral amyloid angiopathy are headache, seizures, personality changes, encephalopathy, and focal neurologic deficits, typically emerging over a period of weeks to months.[45] In the absence of neuropathological confirmation,[42] a diagnosis of probable cerebral amyloid angiopathy–related inflammation[46] can be established on the basis of MRI studies showing single or multiple patches of white-matter hyperintensities involving juxtacortical white matter (Fig. 2E) in patients with hemorrhagic lesions characteristic of probable cerebral amyloid angiopathy. Observational studies suggest that a course of immunosuppressive therapy such as high-dose glucocorticoids can result in clinical and imaging improvement in patients with cerebral amyloid angiopathy–related inflammation[47] and may reduce the likelihood of recurrent disease flares,[48] which makes this an important syndrome to identify.

An intriguing feature of cerebral amyloid angiopathy–related inflammation is its close resemblance to ARIA — an important adverse effect of anti-Aβ immunotherapy for Alzheimer's disease[49] — in its clinical presentation, appearance on neuroimaging, and neuropathological features. It is plausible that ARIA represents an iatrogenic form of spontaneously occurring inflammation related to cerebral amyloid angiopathy, a hypothesis supported by the observation that patients with microbleeds or cortical superficial siderosis who undergo immunotherapy have an increased risk of ARIA.[50] Although these data implicate cerebral amyloid angiopathy as a risk factor for ARIA, current guidelines support the use of anti-Aβ immunotherapy in patients with Alzheimer's disease who have had up to four microbleeds, after a discussion of the potential risks and benefits.[51,52]

CONCLUSIONS AND FUTURE DIRECTIONS

A neuroimaging-based diagnosis of cerebral amyloid angiopathy can inform decisions about blood-pressure control and judicious use or avoidance of antithrombotic therapies. Similar considerations of risks and benefits apply to the incorporation of cerebral amyloid angiopathy markers into decisions about whether to initiate immunotherapy in patients with Alzheimer's disease.

The limited treatment options for cerebral amyloid angiopathy highlight the importance of identifying new approaches to disease modification. The decades-long pathogenic pathway and insidious effects on physiological properties of blood vessel, cognitive function, and intracerebral hemorrhage risk provide a long time window for slowing progression, but only if the early pathogenic steps can be detected and blocked. Potential approaches to slowing the progression of cerebral amyloid angiopathy include reducing Aβ production, enhancing Aβ clearance, and protecting vessels from destructive remodeling triggered by Aβ. Data on blocking production of Aβ may emerge from an ongoing phase 2 trial (ClinicalTrials.gov number, NCT06393712) of a C16-conjugated short interfering RNA[53] targeted to APP, a trial involving persons with symptomatic sporadic cerebral amyloid angiopathy as well as those with presymptomatic or symptomatic Dutch-type cerebral amyloid angiopathy. Determining how and when cerebral amyloid angiopathy can be slowed will inform future progress in developing treatments for this small-vessel brain disease.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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REFERENCES

1. Ness AM, Aiken J. Gustav Oppenheim (1882-1937) and the discovery of cerebral amyloid angiopathy. Neuroscientist 2025;31:225-33.
2. 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;16:30-42.
3. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. Ann Neurol 1991;30:637-49.
4. Kozberg MG, Yi I, Freeze WM, et al. Blood-brain barrier leakage and perivascular inflammation in cerebral amyloid angiopathy. Brain Commun 2022;4:fcac245.

5. 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;18:10-28.
6. Koemans EA, Chhatwal JP, van Veluw SJ, et al. Progression of cerebral amyloid angiopathy: a pathophysiological framework. Lancet Neurol 2023;22:632-42.
7. Kaushik K, van Etten ES, Siegerink B, et al. Iatrogenic cerebral amyloid angiopathy post neurosurgery: frequency, clinical profile, radiological features, and outcome. Stroke 2023;54:1214-23.
8. Jia J, Ning Y, Chen M, et al. Biomarker changes during 20 years preceding Alzheimer's disease. N Engl J Med 2024;390:712-22.
9. Rodrigues MA, Samarasekera N, Lerpiniere C, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. Lancet Neurol 2018;17:232-40.
10. Incontri D, Marchina S, Andreev A, et al. Etiology of primary cerebellar intracerebral hemorrhage based on topographic localization. Stroke 2023;54:3074-80.
11. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 2018;83:74-83.
12. Makkinejad N, Zanon Zotin MC, van den Brink H, et al. Neuropathological correlates of white matter hyperintensities in cerebral amyloid angiopathy. J Am Heart Assoc 2024;13(22):e035744.
13. Soontornniyomkij V, Lynch MD, Mermash S, et al. Cerebral microinfarcts associated with severe cerebral beta-amyloid angiopathy. Brain Pathol 2010;20:459-67.
14. Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. Ann Neurol 2011;69:320-7.
15. Case NF, Charlton A, Zwiers A, et al. Cerebral amyloid angiopathy is associated with executive dysfunction and mild cognitive impairment. Stroke 2016;47:2010-6.
16. Smith EE, Charidimou A, Ayata C, Werring DJ, Greenberg SM. Cerebral amyloid angiopathy-related transient focal neurologic episodes. Neurology 2021;97:231-8.
17. van Etten ES, Kaushik K, van Zwet EW, et al. Sensitivity of the Edinburgh criteria for lobar intracerebral hemorrhage in hereditary cerebral amyloid angiopathy. Stroke 2020;51:3608-12.
18. 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;21:714-25.
19. Charidimou A, Farid K, Baron J-C. Amyloid-PET in sporadic cerebral amyloid angiopathy: a diagnostic accuracy meta-analysis. Neurology 2017;89:1490-8.
20. Charidimou A, Boulouis G. Core CSF biomarker profile in cerebral amyloid angiopathy: updated meta-analysis. Neurology 2024;103(7):e209795.
21. Seiffge DJ, Polymeris AA, Law ZK, et al. Cerebral amyloid angiopathy and the risk of hematoma expansion. Ann Neurol 2022;92:921-30.
22. de Bruin OF, Voigt S, Schoones JW, Moojen WA, van Etten ES, Wermer MJH. Surgical intervention for cerebral amyloid angiopathy-related lobar intracerebral hemorrhage: a systematic review. J Neurosurg 2024;141:955-65.
23. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke 2022;53(7):e282-e361.
24. Steiner T, Purrucker JC, Aguiar de Sousa D, et al. European Stroke Organisation (ESO) and European Association of Neurosurgical Societies (EANS) guideline on stroke due to spontaneous intracerebral haemorrhage. Eur Stroke J 2025;10:1007-86.
25. Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: a meta-analysis. Neurology 2017;89:820-9.
26. Charidimou A, Boulouis G, Roongpiboonsopit D, et al. Cortical superficial siderosis and recurrent intracerebral hemorrhage risk in cerebral amyloid angiopathy: large prospective cohort and preliminary meta-analysis. Int J Stroke 2019;14:723-33.
27. Jia X, Bo M, Zhao H, Xu J, Pan L, Lu Z. Risk factors for recurrent cerebral amyloid angiopathy-related intracerebral hemorrhage. Front Neurol 2023;14:1265693.
28. Charidimou A, Boulouis G, Xiong L, et al. Cortical superficial siderosis and first-ever cerebral hemorrhage in cerebral amyloid angiopathy. Neurology 2017;88:1607-14.
29. Biffi A, Anderson CD, Battey TWK, et al. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. JAMA 2015;314:904-12.
30. O'Donnell HC, Rosand J, Knudsen KA, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med 2000;342:240-5.
31. Veltkamp R, Korompoki E, Harvey KH, et al. Direct oral anticoagulants versus no anticoagulation for the prevention of stroke in survivors of intracerebral haemorrhage with atrial fibrillation (PRESTIGE-AF): a multicentre, open-label, randomised, phase 3 trial. Lancet 2025;405:927-36.
32. Al-Shahi Salman R, Stephen J, Tierney JF, et al. Effects of oral anticoagulation in people with atrial fibrillation after spontaneous intracranial haemorrhage (COCROACH): prospective, individual participant data meta-analysis of randomised trials. Lancet Neurol 2023;22:1140-9.
33. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149(1):e1-e156.
34. Fernando SM, Qureshi D, Talarico R, et al. Intracerebral hemorrhage incidence, mortality, and association with oral anticoagulation use: a population study. Stroke 2021;52:1673-81.
35. Thiankhaw K, Best J, Srivastava S, et al. Left atrial appendage occlusion in patients with atrial fibrillation and intracerebral haemorrhage associated with cerebral amyloid angiopathy: a multicentre observational study and pooled analysis of published studies. J Neurol Neurosurg Psychiatry 2025;96:528-36.
36. Al-Shahi Salman R, Minks DP, Mitra D, et al. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. Lancet Neurol 2019;18:643-52.
37. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.
38. Arima H, Tzourio C, Anderson C, et al. Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy: the PROGRESS trial. Stroke 2010;41:394-6.
39. Chen C-J, Brown WM, Moomaw CJ, et al. Alcohol use and risk of intracerebral hemorrhage. Neurology 2017;88:2043-51.
40. Shoamanesh A, Selim M. Use of lipid-lowering drugs after intracerebral hemorrhage. Stroke 2022;53:2161-70.
41. Jensen MP, Ziff OJ, Banerjee G, Ambler G, Werring DJ. The impact of selective serotonin reuptake inhibitors on the risk of intracranial haemorrhage: a systematic review and meta-analysis. Eur Stroke J 2019;4:144-52.
42. Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy-re-

lated inflammation. Ann Neurol 2004;55:250-6.
43. Salvarani C, Hunder GG, Brown RD Jr. Primary central nervous system vasculitis. N Engl J Med 2024;391:1028-37.
44. 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;73:449-58.
45. Theodorou A, Palaiodimou L, Papagiannopoulou G, et al. Clinical characteristics, neuroimaging markers, and outcomes in patients with cerebral amyloid angiopathy: a prospective cohort study. J Clin Med 2023;12:5591.
46. Auriel E, Charidimou A, Gurol ME, et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. JAMA Neurol 2016;73:197-202.
47. Antolini L, DiFrancesco JC, Zedde M, et al. Spontaneous ARIA-like events in cerebral amyloid angiopathy-related inflammation: a multicenter prospective longitudinal cohort study. Neurology 2021;97(18):e1809-e1822.
48. Regenhardt RW, Thon JM, Das AS, et al. Association between immunosuppressive treatment and outcomes of cerebral amyloid angiopathy-related inflammation. JAMA Neurol 2020;77:1261-9.
49. Greenberg SM, Bax F, van Veluw SJ. Amyloid-related imaging abnormalities: manifestations, metrics and mechanisms. Nat Rev Neurol 2025;21:193-203.
50. Zimmer JA, Ardayfio P, Wang H, et al. Amyloid-related imaging abnormalities with donanemab in early symptomatic Alzheimer disease: secondary analysis of the TRAILBLAZER-ALZ and ALZ 2 randomized clinical trials. JAMA Neurol 2025;82:461-9.
51. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. J Prev Alzheimers Dis 2023;10:362-77.
52. Rabinovici GD, Selkoe DJ, Schindler SE, et al. Donanemab: appropriate use recommendations. J Prev Alzheimers Dis 2025;12:100150.
53. Brown KM, Nair JK, Janas MM, et al. Expanding RNAi therapeutics to extrahepatic tissues with lipophilic conjugates. Nat Biotechnol 2022;40:1500-8.

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