Cerebral amyloid angiopathy

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Originally released May 16, 1997; last updated February 1, 2017; expires February 1, 2020

Introduction

This article includes discussion of cerebral amyloid angiopathy, congophilic angiopathy, cerebrovascular amyloidosis, angiopathy dyshorique, familial amyloidosis, familial oculoleptomeningeal amyloidosis, and hereditary cerebral hemorrhage with amyloidosis. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Cerebral amyloid angiopathy is increasingly recognized as a major cause of hemorrhagic stroke in the elderly as well as an important contributor to the growing challenge of vascular cognitive impairment, even in cerebral amyloid angiopathy patients without hemorrhagic stroke. Among the advances highlighted in this update are: (1) the importance of sulcal bleeding events in early recurrent hemorrhagic stroke in cerebral amyloid angiopathy; (2) the varied clinical presentations and associated neuroimaging profiles of the disease; (3) the cognitive profile of cerebral amyloid angiopathy; (4) the cumulative importance of different pathologic lesions in cerebral amyloid angiopathy that contribute to cognitive decline and the emergence of techniques to measure this cumulative effect by assessing structural connectivity in the disease; (5) the role of impaired vascular reactivity early in disease course; and (6) the role of vascular amyloid in causing cerebral microbleeds in the disease.

Key points

- Cerebral amyloid angiopathy is a common pathology in the aging brain, most often recognized in clinical practice as the cause of multiple, strictly lobar intracerebral hemorrhages, microbleeds, or superficial sulcal/meningeal bleeding.
- Cerebral amyloid angiopathy-related microbleeds and superficial sulcal/meningeal bleeding are sensitively detected by T2*-weighted gradient-echo MRI techniques.
- Advanced cerebral amyloid angiopathy is also associated with nonhemorrhagic brain lesions such as white matter T2-hyperintensities and microinfarcts.
- Reasonable steps for limiting the risk of recurrent cerebral amyloid angiopathy-related hemorrhage are blood pressure control, avoidance of anticoagulation, and withholding of other antithrombotics in the absence of clear-cut indication.
- A subset of cerebral amyloid angiopathy presents with subacute mental status changes, headache, seizures, and amyloid-related vascular inflammation, related in at least some instances to antiamyloid autoantibodies in the cerebrospinal fluid and often improving with immunosuppressive treatment.

Historical note and terminology

Cerebral amyloid angiopathy has been recognized since the early part of this century. In the German literature in 1907 and 1909, Fischer and Oppenheim described cases that, in retrospect, probably were cerebral amyloid angiopathy (Fischer 1910). Early labels for this clinicopathologic condition included “drusige Entartung der Artien und Kapillaren” and “amyloidose cerebrale et meninge.” In 1927, Divry described amyloid in vessel walls and neuritic plaques, based on birefringence when viewed under polarized light with Congo red staining, leading to the term “congophilic angiopathy.” In 1952, Morel and Wildi coined the term “dyshoric angiopathy” to describe vascular amyloid that invades the surrounding parenchyma. In 1935, the occurrence of a familial form of cerebral amyloid angiopathy in Iceland was described by Arnason and later labeled “hereditary cerebral hemorrhage with amyloid—Icelandic type” (Arnason 1935). A second familial form was recognized in the Netherlands in 1964 by Luyendijk and later labeled “hereditary cerebral hemorrhage with amyloid—Dutch type.” Although an association of cerebral amyloid angiopathy with Alzheimer disease was recognized in the 1940s, it was not until the 1970s that Jellinger and others realized that cerebral amyloid angiopathy is an integral part of Alzheimer disease (Jellinger 1977). Also in the 1970s, several groups suggested a relation between cerebral amyloid angiopathy and nontraumatic intracerebral hemorrhage. Perhaps the most pivotal event in the history of cerebral amyloid occurred in 1984 when Glenner and Wong isolated and partially
sequenced the amyloid protein found in meningeal arteries of brains of patients with Alzheimer disease and Down syndrome (Glennner and Wong 1984). In 1987, Pardridge and colleagues isolated and partially sequenced the same amyloid peptide from intraparenchymal arterioles in patients with Alzheimer disease (Pardridge et al 1987). Currently, more than 10 central nervous system diseases have been associated with various forms of cerebral amyloid angiopathy. Over the last decades, interest in cerebral amyloid angiopathy has escalated, spurred by the development of molecular biological techniques and neuroimaging methods to dissect the cerebral amyloidoses, including cerebral amyloid angiopathy-related hemorrhage and Alzheimer disease.

Clinical manifestations

Presentation and course

It is important to distinguish the following disorders related to deposition of amyloid in the central nervous system from the systemic amyloidoses in which amyloid is deposited in the peripheral nervous system and other organs. Although the familial oculoleptomeningeal amyloidoses can affect sites both in and outside the central nervous system, brain and vascular involvement are typically not prominent features of these disorders.

Intracerebral hemorrhage. Cerebral amyloid angiopathy most commonly appears in a sporadic form associated with aging. A classic vascular presentation of sporadic cerebral amyloid angiopathy is lobar hemorrhage, often recurrent or multifocal, in an elderly individual. ( embed=“pagecomponents/media_embed” entry_id=“8003” ) Cerebral amyloid angiopathy has been identified as responsible for 10% to 20% of primary intracerebral hemorrhages in autopsy series and 34% of primary intracerebral hemorrhages in a clinical series drawn from various populations (Itoh et al 1993; Jellinger 2002; Greenberg 2004). The associated hemorrhages often rupture into the subarachnoid space and have been reported to occur frequently at night; these features contrast with hypertensive hemorrhages, which preferentially rupture into the ventricular space and occur during daytime activities. ( embed=“pagecomponents/media_embed” entry_id=“8004” ) In several series, 9% to 53% of clinically significant hemorrhages related to cerebral amyloid angiopathy were multiple.

Controlling for lobar volume, cerebral amyloid angiopathy-related hemorrhage tends to occur most commonly per cc of tissue in the occipital cortex, though all lobes can be affected (Vinters 1987; Rosand et al 2005). Cerebellar and basal ganglia intracerebral hemorrhages secondary to cerebral amyloid angiopathy occur infrequently, and brainstem hemorrhage is extremely rare. Symptomatic subarachnoid hemorrhage or subdural hematoma secondary to cerebral amyloid angiopathy occurs rarely in the absence of intraparenchymal hemorrhage. Subclinical superficial sulcal/meningeal bleeding may be common, however, appearing in 23 of 28 (61%) pathologically proven cases of cerebral amyloid angiopathy (Linn et al 2010), and may be associated with increased risk of recurrent intracerebral hemorrhage (Charidimou et al 2013b; Roongpiboonsopit et al 2016). The locations of cerebral amyloid angiopathy-related brain hemorrhages reflect the distribution of the pathology of cerebral amyloid angiopathy, a microangiopathy that most frequently affects neocortex and the overlying leptomeninges, rarely the cerebellum (including meninges), and almost never the deep hemispheric or brainstem structures (Ni et al 2015b). This pattern of localization helps distinguish cerebral amyloid angiopathy-related intracerebral hemorrhage from the more characteristically deep hemispheric bleeds associated with hypertension.

The clinical features of intracerebral hemorrhage secondary to cerebral amyloid angiopathy include an abrupt onset of headache, focal lobar neurologic deficits, altered level of consciousness, nausea, and vomiting. Head injury and surgical procedures have been anecdotally reported to precipitate intracerebral hemorrhages, though a causal relationship remains to be established. Stronger evidence supports anticoagulant, thrombolytic, or antiplatelet agents as triggers for cerebral amyloid angiopathy-related hemorrhages (Rosand et al 2000; McCarron and Nicoll 2004; Biffi et al 2010a). Individuals with exclusively lobar microbleeds appear to be at increased risk of incidental intracerebral hemorrhage even in the absence of prior intracerebral hemorrhage (van Etten et al 2014; Akoudad et al 2015). Hypertension frequently coexists with cerebral amyloid angiopathy in older populations. Growing evidence suggests that hypertension may increase risk of hemorrhage in cerebral amyloid angiopathy, but further studies in this area are required (Biffi et al 2015).

Other presentations. There is accumulating evidence that sporadic cerebral amyloid angiopathy can present with a variety of clinical profiles other than lobar hematomas. Patients with cerebral amyloid angiopathy may present to memory clinics for evaluation of early cognitive impairment or dementia (Charidimou et al 2015; Boulouis et al 2017). Small hemorrhages or microbleeds in cerebral amyloid angiopathy occur in superficial sulcal/meningeal, cortical, and
subcortical sites, most often without definite clinical manifestations. Some of these individuals, however, develop recurrent, transient neurologic symptoms (Greenberg et al 1993; Raposo et al 2011; Charidimou et al 2012). The symptoms of stereotyped, recurrent, transient neurologic events, acute cortical bleeding events, or spreading depression are characterized by paresthesias, numbness, or weakness with a march over seconds or minutes (Charidimou et al 2012; Ni et al 2015a). An analysis of 25 individuals with transient focal neurologic episodes from a multicenter cohort of 172 individuals diagnosed with cerebral amyloid angiopathy found approximately equal numbers with predominantly positive symptoms (spreading paresthesias, positive visual phenomena, or limb jerking) and negative symptoms (weakness, language impairment, or visual loss) (Charidimou et al 2012). Among those individuals who underwent MRI, chronic supraventricular/meningeal hemorrhage was identified in 50% with transient focal neurologic episodes versus 19% without (p=0.001), suggesting a possible causative role for the superficial blood products in generating these symptoms. Several studies have shown an association between subcortical bleeding events and future intracerebral hemorrhage, raising the possibility that these spells might also be markers for future bleeding (Charidimou et al 2012; Beitzke et al 2015; Ni et al 2015a; Roongpiboonsopit et al 2016).

Accumulating data suggest an association between cerebral amyloid angiopathy and white matter lesions or leukoaraisos. Supporting lines of evidence include: (1) prominent leukoaraiosis in several hereditary forms of cerebral amyloid angiopathy (Bornebroek et al 1996; Grabowski et al 2001); (2) neuropathological correlations between advanced cerebral amyloid angiopathy and white matter disease (Haglund and Englund 2002); and (3) volumetric MRI analysis showing almost twice as much white matter disease in advanced cerebral amyloid angiopathy as in Alzheimer disease or mild cognitive impairment, conditions that are themselves associated with leukoaraiosis (Gurol et al 2006). The association between cerebral amyloid angiopathy and leukoaraiosis is striking, in that cerebral amyloid angiopathy generally spares the small vessels within the regions of white matter pallor. Topographically remote convexity or meningeal cerebral amyloid angiopathy have been suggested to generate leukoaraiosis indirectly by producing hypoperfusion of the white matter through long, pial-penetrating arteries (Gray et al 1985). Like amyloid pathology in the disease, white matter lesions appear to have a posterior predominance in patients with cerebral amyloid angiopathy (Thanprasertsuk et al 2014). The white matter lesion pattern of subcortical spots also appears to be more common in cerebral amyloid angiopathy compared to patients with hypertensive arteriopathy who more commonly harbor peribasal ganglia lesions (Charidimou et al 2016a).

Advanced cerebral amyloid angiopathy also appears to trigger small, clinically asymptomatic ischemic infarcts (van Veluw et al 2016b). In a neuropathological study using microglial immunostaining to detect microinfarcts, these lesions were found to be significantly more common and more numerous in brains with severe rather than mild cerebral amyloid angiopathy (Soontornniyomkij et al 2010). Analysis of living patients by diffusion-weighted MRI reached similar conclusions: small lesions consistent with subacute infarctions were identified in 12 of 78 (15%) with probable cerebral amyloid angiopathy versus 0 of 55 microbleed-free control subjects (Kimberly et al 2009). The lesions were located mostly in cortex and subcortical white matter and were associated with higher numbers of cerebral microbleeds. An analysis of 114 patients with recent intracerebral hemorrhage found diffusion-weighted lesions in 9 of 39 (23%) with probable cerebral amyloid angiopathy versus 6 of 75 (8%) in other types of intracerebral hemorrhage and 0 of 47 age-matched control subjects (Gregoire et al 2011), suggesting a particular association with advanced cerebral amyloid angiopathy. A neuroimaging-neuropathological study has shown that the number of microbleeds on MRI correlates with the number of microinfarcts on pathology (Lauer et al 2016). Determining whether these microinfarcts contribute to clinical neurologic dysfunction is the focus of ongoing studies.

Dilated perivascular spaces (DPVS) are another neuroimaging marker of small vessel disease (SVD) (Heier et al 1989; Rouhl et al 2008; Doubal et al 2010; Zhu et al 2010a; Zhu et al 2010b; Wardlaw et al 2013), and in cerebral amyloid angiopathy in particular (Charidimou et al 2013a; Martinez-Ramirez et al 2013; Charidimou et al 2014). Previous studies on dilated perivascular spaces have generally distinguished between dilated perivascular spaces in the basal ganglia (BG-DPVS) and dilated perivascular spaces in the white matter (WM-DPVS). Several studies have suggested that patients with probable or possible cerebral amyloid angiopathy appear to have a higher prevalence of severe dilated perivascular spaces in the white matter (WM-DPVS) (Charidimou et al 2013a; Martinez-Ramirez et al 2013). Additionally, WM-DPVS appears to correlate with pathologically proven cerebral amyloid angiopathy (Charidimou et al 2014). It has been hypothesized that in patients with cerebral amyloid angiopathy, interstitial fluid blockage due to β-amyloid accumulation within the perivascular space might favor the dilation of these spaces in white matter regions. This may be a result of changes in perivascular drainage due to aging and other factors that contribute to β-amyloid accumulation in patients with cerebral amyloid angiopathy (Hawkes et al 2014). Indeed, neuropathologic evidence suggests that perivascular space dilatation is most severe in areas of high amyloid deposition (van Veluw et al 2016a).
Dementia is frequently encountered in patients with cerebral amyloid angiopathy. In Vinters’ series, over 40% of patients with cerebral amyloid angiopathy-related hemorrhage exhibited dementia (Vinters 1987). Although dementia might be triggered or exacerbated by occurrence of cerebral amyloid angiopathy-related intracerebral hemorrhage, a study of 182 subjects with definite, probable, or possible cerebral amyloid angiopathy found 42 subjects (23%) were cognitively impaired prior to hemorrhage (Smith et al 2004). Several studies have further suggested that the underlying small vessel disease in cerebral amyloid angiopathy, rather than the intracerebral hemorrhage itself, is a predictor of cognitive impairment in the disease (Benedictus et al 2015; Biffi et al 2016; Moulin et al 2016). Smith and colleagues’ study also suggested that cerebral amyloid angiopathy-associated leukoaraiosis was an important mechanism for cognitive impairment in these subjects; severe white matter hyperintensities were present in 60% of subjects with prehemorrhage cognitive impairment, versus 24% of those without. Along with leukoaraiosis, other mechanisms likely to contribute to cognitive impairment in cerebral amyloid angiopathy include lobar hemorrhages, microbleeds, ischemic infarcts, and parenchymal amyloid (ie, Alzheimer disease). Advanced cerebral amyloid angiopathy also appears to cause cognitive impairments in individuals without intracerebral hemorrhage. A clinical-pathological study of 404 community dwelling individuals found that those with moderate to very severe cerebral amyloid angiopathy (79 of 404, 18.8%) had worse performance on measures of perceptual speed and episodic memory, even after controlling for potential confounders such as age and Alzheimer disease pathology (Arvanitakis et al 2011). A study has suggested that cerebral amyloid angiopathy is an important independent predictor of which patients with Alzheimer disease pathology go on to develop dementia. Patients with more severe cerebral amyloid angiopathy had faster rates of cognitive decline (Boyle et al 2015). The cognitive profile of patients with cerebral amyloid angiopathy resembles other types of vascular cognitive impairment, with most prominent deficits in executive function and processing speed (Case et al 2016; Xiong et al 2016). Cognitive impairment in cerebral amyloid angiopathy is likely related to the accumulation of multiple pathologic lesions in the disease, including microbleeds, white matter hyperintensities, and cerebral microinfarctions (Auriel and Greenberg 2012; Auriel et al 2014). In concert, these lesions may disrupt structural connectivity networks in the brain resulting in impairments in cognitive domains such as executive functioning and processing speed as well as reduced gait velocity (Reijmer et al 2015). Furthermore, in patients followed longitudinally (mean follow-up time: 1.3±0.4 years), progression of impairment in structural connectivity networks was associated with worse executive functioning (Beta=0.41, p=0.04) (Reijmer et al 2016).

**Hereditary cerebral amyloid angiopathy.** Several familial forms of cerebral amyloid angiopathy reported to date demonstrate autosomal dominant inheritance. The Icelandic form (hereditary cerebral hemorrhage with amyloidosis-Icelandic type) typically presents in the third decade with multiple intracerebral hemorrhages and progresses to dementia, paralysis, and early mortality (Palsdottir et al 2006). Headache (experienced in 63% of patients) and epilepsy (in 25%) are frequent. As opposed to other forms of cerebral amyloid angiopathy, most hemorrhages in the Icelandic form occur in the basal ganglia. Spinal cord vessels may also be affected. Survival is usually 10 to 20 years from symptom onset.

The Dutch form (hereditary cerebral hemorrhage with amyloidosis-Dutch type) has been described in several families in 2 fishing villages on the North Sea coast of the Netherlands (Zhang-Nunes et al 2006). This form of cerebral amyloid angiopathy has a later onset, in the fourth to sixth decades. Although chronic headaches may precede other symptoms by years, intracerebral hemorrhage is the usual presenting symptom. Another 13% of patients experience ischemic strokes, and white matter ischemic changes are common. Hemorrhages frequently are located in the parietal lobe and often progress. The mortality for the initial hemorrhage is 50% to 70% and is higher in females and when the disorder is paternally transmitted. Neuropsychiatric symptoms or dementia are a constant feature and likely represent a vascular dementia, although an Alzheimer disease-like neuronal degeneration cannot be ruled out. The course can be varied, with some patients showing a relatively benign picture and others experiencing recurrent hemorrhages and death over a short period of time. Evidence suggests that mutation carriers may have decreased levels of Aβ40 and Aβ42 in the CSF prior to the onset of clinical symptoms and thus may be an early biomarker in the disease (van Etten et al 2017). Decreased amyloid levels in the CSF are thought to be caused by increased vascular amyloid deposition in the disease, leading to vessel dysfunction. To further support this hypothesis, there is new evidence that suggests early changes in vascular reactivity in mutation carriers prior to symptom onset (van Opstal et al 2017).

Several other hereditary forms of cerebral amyloid angiopathy have been identified. Continuing the convention of naming the forms according to the location where they were first observed, these include the Flemish, Italian, Arctic, Iowa, and Piedmont forms of hereditary cerebral amyloid angiopathy (Zhang-Nunes et al 2006). Each of the forms has been reported to present clinically as either a dementing illness or (with the exception of the Arctic form) lobar hemorrhage, with onset in approximately the sixth decade. The genetic basis for Dutch-type hereditary disease and
these other forms of cerebral amyloid angiopathy is mutation of the amyloid precursor protein (APP) gene (see the paragraph on Genetics in the Pathogenesis and pathophysiology section of this article). Another set of families identified in France demonstrates a similar combination of dementia with or without hemorrhagic stroke, beginning in the fifth to sixth decade (Rovelet-Lecruix et al 2006). Intriguingly, this hereditary form of disease appears related to duplication rather than mutation of amyloid precursor protein. The effect of gene dosage on amyloid deposition is similarly reflected by the noted association between Down syndrome and both Alzheimer disease and cerebral amyloid angiopathy. Anecdotal reports suggest older patients with Down syndrome are at increased risk of intracerebral hemorrhage (McCarron et al 1998), and amyloid angiopathy has been reported in patients with Down syndrome (Mendel et al 2010; Sabbagh et al 2011). Because Alzheimer dementia develops universally in Down syndrome, it is difficult to determine the independent contribution of cerebral amyloid angiopathy to patients' cognitive decline.

A British kindred has hereditary cerebral amyloid angiopathy that leads to progressive dementia, spasticity, and ataxia (familial British dementia, previously known as familial amyloidosis-British type) (Vidal et al 1999). Inheritance is autosomal dominant. In this form, the entire central nervous system is involved, including white matter, cerebellum, brainstem, and spinal cord. Age of onset is usually in the fifth or sixth decade. Unlike the Dutch and Icelandic forms, hemorrhage is not a prominent feature.

Familial oculoleptomeningeal amyloidosis is described in Japanese, Italian, and North American kindreds (Uitti et al 1988; Ushiyama et al 1991). Clinical presentation varies from 1 kindred to another but can include dementia, ataxia, spasticity, ischemic strokes, seizures, peripheral neuropathy, hemiplegic migraine, myelopathy, blindness, and deafness. Intracerebral hemorrhage is rare. These patients have vascular amyloid deposition in the vitreous and retinal vessels, as well as in the leptomeningeal vessels and other organs, but not in brain parenchymal vessels.

Cerebral amyloid angiopathy-related inflammation. Growing numbers of patients have been reported with vascular inflammation associated with advanced cerebral amyloid angiopathy (Eng et al 2004; Scolding et al 2005). These patients typically present with subacute mental status changes, headaches, and seizures, typically at a slightly younger age than those presenting with cerebral amyloid angiopathy-related intracerebral hemorrhage. Characteristic imaging findings are prominent, often asymmetric, white matter lesions with the MRI appearance of edema (hyperintense on T2-weighted sequences, increased diffusivity) that can extend to the overlying cerebral cortex (Kinnecom et al 2007). These clinical and neuroimaging criteria alone have a high sensitivity (82%) and specificity (95%) and can be used reliably to make the diagnosis of cerebral amyloid angiopathy-related inflammation (Auriel et al 2016).

Table 1. Criteria for Diagnosis of Cerebral Amyloid Angiopathy-Related Inflammation

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<th>Probable CAA-related inflammation</th>
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<tr>
<td>1. 40 years of age or older.</td>
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<td>2. At least 1 of the following clinical features: headache, mental status or behavioral change, focal neurologic signs, and seizures. Presentation not directly attributable to an acute ICH.</td>
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<td>3. MRI shows either unifocal or multifocal WMH lesions (cortico-subcortical or deep) that are asymmetric and extend to the immediately subcortical white matter. The asymmetry is not due to past ICH.</td>
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<tr>
<td>4. At least 1 cortical/subcortical hemorrhagic lesion: macrohemorrhage or microhemorrhage or cortical superficial siderosis.</td>
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CAA: cerebral amyloid angiopathy, WMH: white matter hyperintensities, ICH: intracerebral hemorrhage
Patients with this presentation often improve both clinically and radiographically to immunosuppressive therapy, making this potentially the most therapeutically responsive subtype of cerebral amyloid angiopathy. The neuropathological appearance of cerebral amyloid angiopathy-related inflammation suggests that it represents an immune response to the vascular amyloid deposits. An autoimmune etiology has been further supported by the finding of high levels of antiamyloid autoantibodies in the cerebrospinal fluid of 10 individuals with probable cerebral amyloid angiopathy-related vascular inflammation (Chung et al 2011) during the acute phase of the illness compared to several different control groups, including patients diagnosed with noninflammatory amyloid angiopathy or multiple sclerosis. Interestingly, as the patients with cerebral amyloid angiopathy-related inflammation entered remission after immunosuppressive treatment, autoantibodies returned to control levels (Piazza et al 2013).

Prognosis and complications

The outcome of acute lobar hemorrhage related to cerebral amyloid angiopathy appears similarly poor as that resulting from deep hemispheric hemorrhage related to hypertension. Both are associated with 3-month mortalities of approximately 25% and good outcomes (no or moderate disability) in only approximately 30% (Rosand et al 2004). Although lobar hemorrhage may be less likely than deep hemispheric hemorrhages to involve critical brainstem structures, this favorable feature is balanced by the tendency for lobar hemorrhages to be larger and to affect older victims. Mortality is particularly high (approximately 50%) in those hemorrhages occurring during anticoagulation.

Those who survive the initial hemorrhage remain at risk for recurrent hemorrhages, seizures, and cognitive deterioration. The cumulative rate of recurrent hemorrhage in survivors of lobar hemorrhage has been estimated at 21% over 2 years (O'Donnell et al 2000). Predictors of higher risk for early recurrence are: (1) history of a previous hemorrhage prior to the index presenting intracerebral hemorrhage; (2) possession of an apolipoprotein E2 or E4 allele (see Genetics subheading of Pathogenesis and pathophysiology section); (3) a larger number of hemorrhagic lesions counted on gradient-echo MRI scan. In a study of 94 consecutive subjects with gradient-echo MRI at the time of lobar intracerebral hemorrhage, the 3-year cumulative risks for recurrent intracerebral hemorrhage were 14% for those with only 1 hemorrhage (ie, the presenting lesion) on MRI, 17% for those with 2 hemorrhagic lesions at baseline, 38% for those with 3 to 5 hemorrhages, and 51% for subjects with more than 5 hemorrhages (Greenberg et al 2004); and (4) superficial siderosis (Charidimou et al 2013b; Koo et al 2016).

Superficial siderosis appears to also be associated with very early recurrent events in hemorrhage survivors (ie, recurrent event occurs within 6 months of index hemorrhage) (Roongpiboonsopit et al 2016). There is some evidence that posteriorly located white matter damage and antiplatelet agents may increase intracerebral hemorrhage recurrence in patients with cerebral amyloid angiopathy (Biffi et al 2010a).

Clinical vignette

A 65-year-old, right-handed man with history of multiple controlled vascular risk factors (diabetes mellitus, hypertension, hyperlipidemia) presented with acute onset of difficulty reading. He had a history of vague spells of word-finding difficulty in the previous year, as well as slightly increased forgetfulness, but remained fully functional and intellectually active. At the time of his symptoms, he was taking aspirin 81 mg daily, an oral hypoglycemic, an antihypertensive, and a statin. The family history was notable for dementia in the mother in her 70s and otherwise negative for stroke or other neurologic disease. Despite some ongoing complaints of mild difficulty reading, the neurologic exam showed no focal deficits and normal cognition, with 0 errors on the Blessed Dementia Information-Memory-Concentration subscale.

Gradient-echo MRI sequences obtained 3 and 11 months after presentation demonstrated a subacute to chronic left occipital hematoma. These images also showed approximately 20 chronic hemorrhages or microbleeds, primarily in the left occipital and parietal lobes, but also involving the right occipital lobe. Moderately severe white matter hyperintensities were evident on T2-weighted sequences. There was no suggestion of mass lesion or vascular malformation underlying the hemorrhages, and a full laboratory examination disclosed no other cause of hemorrhage such as coagulopathy. The patient was diagnosed with probable cerebral amyloid angiopathy-related hemorrhage based on the finding of multiple strictly lobar hemorrhages without other definite cause.

The patient returned fully to his neurologic and functional baseline following his hemorrhagic stroke. Aspirin was
stopped at the time of the acute hemorrhage but, based on the presence of multiple vascular risk factors, was restarted at 81 mg daily. The statin was continued for similar reasons. The antihypertensive medication was increased with the goal of bringing the blood pressure towards the low end of the normal range as tolerated. The patient was instructed not to use anticoagulants or drink heavily and otherwise to pursue all of his customary physical and mental activities.

**Biological basis**

**Etiology and pathogenesis**

The underlying explanation for why particular individuals without family history develop advanced degrees of amyloid deposition in cerebral blood vessels remains uncertain. In the absence of identified environmental risk factors, genetic factors seem likely, presumably multiple genes interacting in a complex manner. Supporting this possibility is the strong effect of family history on risk of lobar intracerebral hemorrhage (Woo et al 2002). In hereditary cerebral amyloid angiopathy, genetic protein defects trigger the accumulation of beta-pleated sheet fibrils in cerebral vessels.

"Amyloid" is a general term for insoluble proteinaceous material composed of beta-pleated sheet fibrils. Different forms of amyloid occur in a variety of diseases and are deposited in different parts of the body; the beta-pleated sheet is a constant feature of all forms. Amyloids are typically resistant to proteolysis and have affinity for certain dyes. The predominant form of amyloid in sporadic cerebral amyloid angiopathy and the hereditary forms caused by mutation or duplication of amyloid precursor protein is the beta-amyloid peptide (Aβ). The other hereditary forms of cerebral amyloid angiopathy are characterized by distinct forms of amyloid deposits and are discussed further in this section.

**Molecular biology.** Amyloid beta protein (Aβ) is a hydrophobic, nonglycosylated peptide of 39 to 43 amino acids derived from the amyloid precursor protein encoded by a 19-exon gene located on the long arm of chromosome 21. The amyloid precursor protein is a 659- to 770-amino acid residue, membrane-associated glycoprotein processed by secretase enzymes to yield various fragments, including amyloid beta protein. Subtle biochemical differences distinguish the vascular amyloid of cerebral amyloid angiopathy from parenchymal amyloid deposits (eg, amyloid plaques in Alzheimer disease). Vascular amyloid is predominantly composed of the 39- to 40-amino acid amyloid beta protein species (Aβ40), whereas plaque amyloid is predominantly composed of a 42- to 43-amino acid amyloid beta protein species (Aβ42).

**Pathophysiology.**

**Aggregation.** The central pathophysiologic biochemical event in the cerebral amyloidoses is the aggregation of soluble subunit proteins into progressively larger, less soluble, and more biologically active structures. Studies of synthetic amyloid beta protein species demonstrate a tendency to self-aggregate to fibrils in vitro, a predilection more pronounced in Aβ42 fragments than Aβ40. Mutant peptides mimicking the codon 693 or 694 point mutation linked to the Dutch, Italian, Arctic, or Iowa types of hereditary cerebral hemorrhage with amyloidosis exhibit increased beta-sheet content, increased amyloidogenicity, and enhanced fibril stability. Factors favoring in vivo beta-amyloid formation include: (1) overproduction or increased levels of amyloid precursor (as in gene overdose in trisomy 21 Down disease or amyloid precursor protein duplication); (2) a highly amyloidogenic sequence (as in the codon 693 or 694 mutations); (3) altered proteolysis of the amyloid precursor (as in familial Alzheimer disease due to codon 692 mutation); (4) a seeding nucleation event analogous to seeding in crystal formation (Meyer-Luehmann et al 2006); (5) reduced clearance of brain amyloid (also suggested to occur with mutant forms of amyloid beta protein) (Deane et al 2004); and (6) time. Finally, there is mounting evidence that decreases in cerebral blood flow could lead to increased amyloid deposition in cerebral amyloid angiopathy. This may be related to changes in amyloid clearance pathways associated with decreases in cerebral blood flow (Garcia-Alloza et al 2011; Li et al 2014).

**Production and clearance of brain amyloid beta protein.** A variety of theories regarding the source of cerebrovascular amyloid beta protein have been proposed over the years, including the possibility that it is derived from the systemic blood circulation or produced locally within brain blood vessels. There is some evidence that peripherally formed amyloid beta protein may influence cerebral amyloid deposition (Eisele et al 2010; Sutcliffe et al 2011). However, the prevailing model based on current data posits that amyloid beta protein is generated primarily by neurons, diffuses through the brain parenchyma (where it may deposit as the senile plaques of Alzheimer disease), and ultimately accompanies the brain interstitial fluid to the periarterial space (Weller et al 1998). From the periarterial space, amyloid beta protein may either deposit on vessel walls as cerebral amyloid angiopathy or be cleared from the brain.
via efflux transport across the blood-brain barrier, proteolytic degradation, or centrifugal flow of interstitial fluid out of the brain (Schley et al 2006; Boche et al 2008; Carare et al 2008; Morris et al 2016).

The following are among the experimental observations supporting this paradigm: (1) neuronal expression of amyloid precursor protein in transgenic mice is sufficient to produce robust cerebral amyloid angiopathy (demonstrating that amyloid beta protein produced by neurons can reach the vessels); (2) the earliest site of vascular amyloid beta protein deposition is located in proximity to the periartrial space, at the junction of the media and adventitia; (3) there is reduced clearance by efflux transport of the mutant forms of amyloid beta protein that tend to accumulate in vessels; (4) shifting the population of amyloid beta protein from Aβ40 to Aβ42 by coexpression of mutant presenilin-1 causes more of the peptide to deposit as senile plaques and less to reach the periartrial space and deposit in vessels (Herzig et al 2006); and (5) genetic reduction or elimination of the protease nephrilysin causes cerebral amyloid angiopathy to appear in a transgenic mouse model that otherwise does not develop cerebral amyloid angiopathy at a comparable age (Farris et al 2007). Important implications of this model are that cerebral amyloid angiopathy progression might be slowed by agents that lower its production, decrease its tendency to aggregate in the periartrial space, or stimulate its degradation, or enhance its clearance across the blood-brain barrier. Although many of these predictions remain to be tested in mouse models and humans with cerebral amyloid angiopathy, a phase 2 multicenter, randomized control trial testing the effect of antiamyloid immunotherapy on blood vessel function in patients with cerebral amyloid angiopathy has been completed and data are pending (http://clinicaltrials.gov/show/NCT01821118). Data testing this same antiamyloid immunotherapy in mice has suggested that it can both remove vascular amyloid deposits and improve vascular reactivity in animals (Bales et al 2016).

Pathogenesis of hemorrhage. Clinicopathologic studies identify several mechanisms through which patients with cerebral amyloid angiopathy may develop microvascular weakening leading to lobar and subarachnoid hemorrhage. Heavily amyloid-laden microvessels appear structurally brittle, with reduced fibrillary collagen in the vascular extracellular matrix, and potentially vulnerable to rupture (Zhang et al 1998). Maeda and colleagues found spindle-shaped microaneurysms in small cortical arteries with severe amyloid deposition (Maeda et al 1993). They suggested that (1) amyloid deposition leads to medial and adventitial damage; (2) vessel wall damage leads to microaneurysm formation; (3) plasma components invade the vessel wall leading to areas of fibrinoid necrosis; and (4) hemorrhage develops from rupture of microaneurysm. The finding by Vonsattel and colleagues that, among 17 brains with cerebral amyloid angiopathy, fibrinoid necrosis was present only in the 12 cases with hemorrhage supports the hypothesis that fibrinoid necrosis is the final common denominator determining whether hemorrhage will develop in cases of cerebral amyloid angiopathy (Vonsattel et al 1991). However, pathologic evidence appears to show that microbleeds occur in areas distant from amyloid-laden blood vessels, with reduced amyloid burden at the actual sites of microbleeds. This finding may suggest that rather than a direct effect, vascular amyloid deposition might exert more regional changes in vascular blood flow that compromise the integrity of the microvascular network (van Veluw et al 2017). One additional mechanism by which amyloid beta protein may promote intracerebral hemorrhage is by increased local anticoagulant activity; fibrillar amyloid beta protein has been found to bind amyloid precursor protein and potentiate its inhibition of clotting factor Xla (Wagner et al 2000).

Genetics.

Hereditary cerebral amyloid angiopathy. The hereditary cerebral amyloid angiopathies with amyloid beta protein deposition are all associated with alterations of the amyloid precursor protein gene. The gene for amyloid precursor protein resides on the long arm of chromosome 21 and contains 19 exons. The amyloid beta protein fragment of amyloid precursor protein is encoded by parts of exon 16 and 17. The Dutch, Flemish, Italian, Arctic, Iowa, and Piedmont forms of hereditary cerebral amyloid angiopathy are each associated with single nucleotide mutations within the amyloid beta protein-coding region of amyloid precursor protein, resulting in single amino acid changes in amyloid beta protein (Table 1):{embed="pagecomponents/media_embed" entry_id="8006"} The French hereditary form of cerebral amyloid angiopathy is associated with duplication of the amyloid precursor protein gene.

The location of the amyloid precursor protein mutations associated with prominent cerebral amyloid angiopathy contrasts with the amyloid precursor protein mutations associated primarily with familial Alzheimer disease, located immediately flanking rather than within the amyloid beta protein-coding regions. The majority of cases of familial Alzheimer disease are caused by defects in the presenilin genes located on chromosomes 14 (presenilin-1) and 1 (presenilin-2). Advanced cerebral amyloid angiopathy can occur in familial Alzheimer disease due to these gene defects but, in general, is not prominent.
Among nonamyloid beta protein forms of hereditary cerebral amyloid angiopathy, the Icelandic type of hereditary cerebral hemorrhage with amyloidosis is transmitted in autosomal dominant fashion. The cystatin C protein in affected patients lacks the first 10 amino acids and has a Glu-for-Leu substitution at residue 68. The gene for cystatin C lies on chromosome 20p11.2 and contains 3 exons. All patients with genetic analysis reported to date have demonstrated a single T-2-A transversion in codon 68. Familial oculoleptomeningeal amyloidosis is transmitted in autosomal dominant fashion. Like the more general class of familial amyloid polyneuropathies, these disorders are associated with mutations of the transthyretin gene located on chromosome 18. As multiple distinct transthyretin point mutations have been reported to associate with oculoleptomeningeal involvement in at least some families, the genotype-phenotype correlation of this spectrum of disorders remains to be worked out. The genetic cause of familial British dementia has been identified as mutational loss of a stop codon within the BRI gene on chromosome 13 (Vidal et al 1999). The absence of the normal stop codon leads to generation of an insoluble 34 amino acid cleavage product that comprises the vascular amyloid deposits in this disorder.

Sporadic cerebral amyloid angiopathy. The major genetic risk factor for sporadic cerebral amyloid angiopathy (as well as sporadic Alzheimer disease) is the apolipoprotein \( E \) gene. Apolipoprotein \( E \) is located on chromosome 19q13.2, and exists in 3 major allelic variants differing by single nucleotide and amino acid differences: \( E2 \), \( E3 \), and \( E4 \). Both the apolipoprotein \( E2 \) and \( E4 \) alleles appear to increase the risk of cerebral amyloid angiopathy-related intracerebral hemorrhage. This situation contrasts with Alzheimer disease, where \( E4 \) increases risk but \( E2 \) decreases risk. The reason for this discrepancy appears to lie in differences between the cerebral amyloid angiopathy and Alzheimer disease processes: Apolipoprotein \( E4 \) enhances deposition of amyloid beta protein in both vessels and senile plaques, whereas apolipoprotein \( E2 \) promotes the breakdown of amyloid-laden vessels, a step that is unique to the cerebral amyloid angiopathy pathway (Greenberg et al 1998; McCarron et al 1999a). Pathologic studies have suggested that having the apolipoprotein \( E4 \) allele appears to increase severity of cerebral amyloid angiopathy (Yu et al 2015). Although the apolipoprotein \( E2 \) genotype appears to be more common in cerebral amyloid angiopathy patients with intracerebral hemorrhage, the apolipoprotein \( E4 \) genotype is more common in patients with cognitive impairment (Charidimou et al 2015).

A population-based study of hemorrhagic stroke in the greater Cincinnati/northern Kentucky region found possession of an \( E2 \) or \( E4 \) allele to confer 2.3-fold increased odds for lobar hemorrhage (Woo et al 2002). The 29% attributable risk associated with apolipoprotein \( E \) genotype made it the single greatest attributable risk factor for lobar hemorrhage in this study. An analysis of 2189 individuals with intracerebral hemorrhage and 4041 control subjects drawn from 7 international centers confirmed associations of lobar hemorrhage with apolipoprotein \( E2 \) (odds ratio 1.82) and \( E4 \) (odds ratio 2.2) at the extremely high levels of statistical significance typically used in genome-wide association studies (\( p<1 \times 10^{-9} \) for both alleles) (Biffi et al 2010b). The same alleles are also associated with earlier hemorrhage recurrence. In a prospective study of 71 consecutive elderly patients who survived lobar hemorrhage, those who carried apolipoprotein \( E2 \) or \( E4 \) had a 2-year cumulative rate of recurrence of 28% compared to 10% for those with the common apolipoprotein \( E3/E3 \) genotype (O'Donnell et al 2000). The \( E2 \) allele further confers risk for larger hemorrhage volumes and worse outcomes following lobar intracerebral hemorrhage (Biffi et al 2011) suggesting specific effects of this genetic variant on the vascular structure in cerebral amyloid angiopathy.

Even adjusting for apolipoprotein \( E \) genotype, family history of hemorrhagic stroke remains another risk factor for lobar hemorrhage (Woo et al 2002). A novel candidate genetic factor is the CR1 gene rs6656401 polymorphism, which was found to be associated with cerebral amyloid angiopathy-related lobar hemorrhage (odds ratio 1.61), risk of recurrent hemorrhage (hazard ratio 1.35), and severe cerebral amyloid angiopathy pathology at autopsy (odds ratio 1.34) (Biffi et al 2012). Heritability estimates suggest that, beyond the apolipoprotein \( E \) genotype, there is a substantial genetic contribution to risk of intracerebral hemorrhage in cerebral amyloid angiopathy (Devan et al 2013). Future studies are, thus, likely to identify further genetic risks for sporadic cerebral amyloid angiopathy.

Neuropathology. Cerebral amyloid angiopathy pathology is common in normal, asymptomatic elderly individuals. Tomonaga found an incidence of 36% in an autopsy series of normal brains (Tomonaga 1981). The incidence in normals increases with age. The prevalence of cerebral amyloid angiopathy pathology is even higher in the presence of accompanying Alzheimer disease (Yamada et al 1987). Cerebral amyloid angiopathy is noted in up to 92% of brains from Alzheimer disease patients and is widely accepted as 1 of 4 microscopic features that, when present in abundance, allow for the neuropathologic diagnosis of Alzheimer disease. It is nonetheless important to note that cerebral amyloid angiopathy can occur without other Alzheimer pathologies, and Alzheimer disease can occur without evidence of cerebral amyloid angiopathy. Patients with combined Alzheimer disease and cerebral amyloid angiopathy...
are at risk for lobar hemorrhage in addition to dementia. Evidence suggests that patients with Alzheimer disease and cerebral amyloid angiopathy appear to have an increased frequency of transient neurologic episodes (Ringman et al 2014). These symptoms might help identify patients with the disease without lobar hemorrhage in memory clinic populations. In a neuropathologic study of 117 brains with definite Alzheimer disease, the one quarter with moderate to severe cerebral amyloid angiopathy had a higher incidence of hemorrhages and ischemic lesions than those with less severe or absent cerebral amyloid angiopathy (Ellis et al 1996).

Cerebral amyloid angiopathy can be strongly suspected in brain tissue by examination of routine (hematoxylin- and eosin-stained) sections. Under routine staining, cerebral amyloid angiopathy appears in cortical microvessels as an effacement of the normal arteriolar smooth muscle cell component, which is replaced by a hyaline eosinophilic material. Its existence and extent can be confirmed by using cytochemical techniques, such as Congo red with polarization microscopy and thioflavin S or T with fluorescence microscopy. Although immunohistochemical techniques are more specific, conventional cytochemical methods (eg, Congo red) are still valuable tools for screening brain tissue removed at autopsy or biopsy for the presence of cerebral amyloid angiopathy.

For definitive identification of cerebral amyloid angiopathy, histochemical methods have been largely superseded by immunohistochemical staining with primary antibodies to the major amyloid proteins: amyloid beta protein (for sporadic cerebral amyloid angiopathy or familial disease involving amyloid precursor protein mutation) or the specific protein deposits characteristic of other hereditary cerebral amyloid angiopathy syndromes such as transthyretin and cystatin C. Most antibodies work well in paraffin-embedded (therefore archival) material, and many excellent primary antibodies are commercially available. Of interest is the observation that anti-cystatin C antibodies also show some labeling of vascular amyloid in sporadic cerebral amyloid angiopathy (Vinters et al 1990).

Some patients with severe cerebral amyloid angiopathy develop superimposed cerebral amyloid angiopathy-related microangiopathies, including microaneurysm formation, fibrosis, a "lumen within a lumen" appearance, and fibrinoid necrosis (Mandybur 1986; Natte et al 1998). Fibrinoid necrosis especially has been implicated in the occurrence of (fatal) cerebral amyloid angiopathy-related intracerebral hemorrhages (Vonsattel et al 1991). Ultrastructural studies of cerebral amyloid angiopathy, though few (because optimally preserved biopsy material is usually required for definitive interpretation of findings), show destruction of smooth muscle cells in affected arterioles, with deposition of characteristic 7 to 10 nm amyloid filaments in place of the smooth muscle and surrounding or encasing remaining smooth muscle cells. Surprisingly, the endothelium appears relatively normal in some instances of arteriolar cerebral amyloid angiopathy (Vinters et al 1994), though it may be severely damaged in the case of capillary amyloid deposition.

In cases of cerebral amyloid angiopathy-related vascular inflammation, the vascular amyloid is associated with a perivascular inflammatory response or true transmural vasculitis, often of a giant-cell type. In these individuals, a variably severe granulomatous inflammatory response develops in response to the cerebral amyloid angiopathy. The inflammatory response includes macrophage and T-cell components (CD4+ and CD8+ cells), and both leptomeningeal and cortical parenchymal microvessels may be involved. Adjacent brain parenchyma usually shows infarcts or microhemorrhages.

**Epidemiology**

Primary intracerebral hemorrhages account for 10% of all strokes in Western populations and a higher proportion among Asians. Clinical and autopsy series from different populations suggest cerebral amyloid angiopathy is responsible for 10% to 34% of these intracerebral hemorrhages (Itoh et al 1993; Greenberg 2004). The mean age of patients with cerebral amyloid angiopathy-related hemorrhages is in the 70s.

The most important risk factor for sporadic cerebral amyloid angiopathy is age. In an autopsy study of 128 subjects, Tomonaga found cerebral amyloid angiopathy in 8% of subjects in the 7th decade of life, 20% in the 8th, 37% in the 9th, and 58% in the 10th, with an overall incidence of 36% of normal subjects aged 60 to 97 (Tomonaga 1981). Sporadic cerebral amyloid angiopathy is rarely seen in persons less than 50 years old. There is no definite age-adjusted gender predilection of cerebral amyloid angiopathy. Some early studies reported a female predominance, but this likely reflected an older mean age of women in these series. With the exception of the hereditary forms of cerebral
Among other potential risk factors for hemorrhagic stroke, although hypertension does not appear essential for hemorrhages caused by cerebral amyloid angiopathy (Woo et al 2002), antihypertensive treatment appears to reduce their occurrence (Woo et al 2005; Arima et al 2010). It has been shown that in an observational study elevated blood pressure is associated with increased recurrent lobar intracerebral hemorrhage risk in patients with probable or possible cerebral amyloid angiopathy (Biffi et al 2015). These results seem in line with animal data that suggests that elevated blood pressure causes hemorrhage with decreased latency in amyloid transgenic mice compared to normal mice (Passos et al 2016). A study has shown that total small vessel disease burden in cerebral amyloid angiopathy (approximated by combining the most common neuroimaging features in the disease) correlated with presence of vasculopathic changes on pathology (a hallmark sign of severity) and presentation with intracerebral hemorrhage (OR 2.40 [95% CI 1.06-5.45], p=0.035 and 2.23 [95% CI 1.07-4.64], p=0.033, respectively) (Charidimou et al 2016b). Neither diabetes mellitus nor coronary atherosclerosis, also prominent vascular risk factors, appears linked to cerebral amyloid angiopathy-related intracerebral hemorrhage. Other potential risks for lobar hemorrhage identified in epidemiological studies are previous ischemic stroke, frequent alcohol use, and low serum cholesterol. It remains unclear whether these factors link specifically to cerebral amyloid angiopathy-related hemorrhages.

The role of genetic factors and family history as risks for cerebral amyloid angiopathy and lobar intracerebral hemorrhage is discussed in the Pathogenesis and pathophysiology section of this article.

**Differential diagnosis**

The differential diagnosis for the intracerebral hemorrhage lesions associated with cerebral amyloid angiopathy includes the following:

- Malignant hypertension
- Hypertensive hemorrhage
- Arteriovenous malformations
- Cavernous hemangiomas
- Hemorrhage into cerebral neoplasms
- Trauma
- Vasculitis
- Coagulopathies
- Mycotic aneurysms
- Cerebral venous thrombosis

The differential diagnosis for the advanced white matter disease that can result from cerebral amyloid angiopathy includes:

- Hypertensive vasculopathy
- Diffuse arteriosclerosis
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Fabry disease
- Moyamoya
- Fibromuscular dysplasia

**Diagnostic workup**

The diagnosis of cerebral amyloid angiopathy is often strongly suspected because of the distinctive clinical picture of recurring lobar hemorrhages in an elderly individual, especially if a history of hypertension is absent. Rendering a firm diagnosis of cerebral amyloid angiopathy is difficult, however, as definitive diagnosis requires a pathologic specimen. The Boston Criteria for diagnosis of cerebral amyloid angiopathy were designed to deal with this situation by recognizing various levels of diagnostic certainty (Knudsen et al 2001). Diagnoses of definite cerebral amyloid angiopathy or probable cerebral amyloid angiopathy with supporting pathology, the highest levels of diagnostic certainty, require full postmortem exam showing pathologically severe cerebral amyloid angiopathy (for definite cerebral amyloid angiopathy) or a sample of brain tissue obtained by biopsy or hematoma evacuation showing some degree of cerebral amyloid angiopathy (for probable cerebral amyloid angiopathy) without other diagnostic lesion.
the more commonly encountered clinical situation when brain tissue is unavailable, the diagnosis of probable cerebral amyloid angiopathy can be reached by radiographic demonstration of multiple, strictly lobar hemorrhages of any size without other definite cause of hemorrhage such as excessive anticoagulation (International Normalized Ratio > 3.0), antecedent head trauma or ischemic stroke, brain tumor, vascular malformation, vasculitis, blood dyscrasias, or coagulopathy. These criteria emanate from the most distinctive features of cerebral amyloid angiopathy-related hemorrhages: their tendency to be multiple, recurrent, and localized to cortical or corticosubcortical (ie, lobar) rather than deep hemispheric brain regions. In validating studies, 13 of 13 diagnoses of probable cerebral amyloid angiopathy were corroborated by neuropathologic exam, suggesting reasonably high specificity (Knudsen et al 2001) and sensitivity was very high among clinically symptomatic patients known to carry the mutation for Dutch hereditary cerebral amyloid angiopathy (van Rooden et al 2009). The diagnostic sensitivity of the Boston Criteria probable cerebral amyloid angiopathy category may be further increased by including the presence of radiographically detected superficial sulcal/meningeal blood products as an additional site of bleeding when determining whether multiple hemorrhages are present (Linn et al 2010). The diagnosis of possible cerebral amyloid angiopathy is used for situations that are less suggestive, such as a single lobar hemorrhage without other definite cause. Validation of these criteria has been further extended to include patients with lobar microbleeds in the absence of intracerebral hemorrhage (Martinez-Ramirez et al 2015). It should be stated that although these criteria appear to have a high positive predictive value for cerebral amyloid angiopathy in patient cohorts, this study suggests that microbleeds alone may have less predictive value for cerebral amyloid angiopathy in population-based cohorts.

Identification of probable or possible cerebral amyloid angiopathy depends on imaging of hemorrhages, which may be acute or chronic, and may represent sizable symptomatic hemorrhage or small (< 0.5 cm diameter) asymptomatic microbleeds. Acute lobar intracerebral hemorrhage is most commonly diagnosed with CT scan. MRI and MRA scans add supportive evidence for the presence of cerebral amyloid angiopathy. MR images exclude an underlying tumor or vascular malformation more definitively than CT. Moreover, MRI allows use of gradient refocused echo sequences (variously referred to as gradient-echo, magnetic susceptibility, or T2-weighted) that are particularly helpful because of their sensitivity to hemosiderin deposits from old hemorrhages, large or small. Gradient-echo MRI is particularly well suited to identify the multiple lobar hemorrhagic lesions required to meet criteria for probable cerebral amyloid angiopathy and increase the level of diagnostic certainty. Greenberg and colleagues obtained MRI gradient-echo sequences in 15 patients with single lobar hemorrhages visualized on CT; 9 showed petechial hemorrhages in additional cortical locations suggestive of cerebral amyloid angiopathy (Greenberg et al 1996). It should be noted that gradient-echo MRI is sensitive to deoxyhemoglobin as well as hemosiderin, making it an effective technique for diagnosis of acute as well as chronic hemorrhage (Kidwell et al 2004). Cerebral angiography does not aid the diagnosis of cerebral amyloid angiopathy except more firmly ruling out other underlying vascular disorders.

The emerging approach of imaging Aβ deposits in vivo with high-affinity ligands developed for Alzheimer disease has shown promise as well for imaging the vascular Aβ deposits of cerebral amyloid angiopathy (Klunk et al 2004). Two studies of PET imaging using Pittsburgh Compound B (PiB) performed on subjects with probable cerebral amyloid angiopathy found significantly increased PiB uptake relative to healthy elderly control subjects and a significantly elevated ratio of occipital-to-global PiB uptake relative to subjects with Alzheimer disease (Johnson et al 2007; Ly et al 2010). Further studies have also indicated increased PiB retention at both current sites of cerebral amyloid angiopathy-related hemorrhagic lesions (Diersken et al 2010) and at sites of future bleeding in subjects who underwent follow-up MRI a median of 19 months after PiB-PET (Gurol et al 2012). Although PiB-PET remains strictly a research tool, these results raise the possibility that noninvasive amyloid imaging might provide diagnostic information for cerebral amyloid angiopathy as well as a marker of sites at increased risk of hemorrhage. The FDA-approved amyloid ligand Florbetapir has been shown to distinguish cerebral amyloid angiopathy-related hemorrhage from hypertensive hemorrhage, opening the question as to whether this tool could be used clinically to diagnosis cerebral amyloid angiopathy in select cases (Gurol et al 2016).

MRI studies of patients with Alzheimer disease (Cordonnier et al 2006; Pettersen et al 2008) and community-dwelling population-based elderly (Jeerakathil et al 2004; Sveinbjörnsdóttir et al 2008; Vernooij et al 2008) have identified a substantial proportion with lobar microbleeds suggestive of possible subclinical cerebral amyloid angiopathy. Among the features that indirectly support the possibility of underlying cerebral amyloid angiopathy were the occipital predominance of the microbleeds seen in Alzheimer patients (Pettersen et al 2008) and the overrepresentation of the apolipoprotein E4 allele among those population-based elderly with microbleeds restricted to lobar brain regions.
A population-based study has shown that individuals with lobar microbleeds are more likely to have cognitive impairment, especially in visuospatial executive function (Chung et al. 2016). Other population-based data further suggest that individuals with more than 4 lobar located microbleeds may be at increased risk for cognitive decline (Akoudad et al. 2016). Further clinical, radiological, and pathological correlation studies will be required to determine whether these lobar microbleeds indeed represent a subclinical form of advanced cerebral amyloid angiopathy and, most importantly, whether their presence should affect clinical decision making.

Neuropathological verification of cerebral amyloid angiopathy is most commonly accomplished by examination of tissue obtained from the wall of an evacuated lobar hematoma or postmortem exam. Brain biopsy is usually not pursued when clinical suspicion of cerebral amyloid angiopathy is high, as confirming a clinically probable diagnosis generally does not lead to major alterations in therapy. The exception to this situation is often those subjects with cerebral amyloid angiopathy-related inflammation, where biopsy can both establish a firm basis for immunosuppressive treatment and exclude other potential causes of brain inflammation. A brain specimen obtained for suspected cerebral amyloid angiopathy should include leptomeningeal tissue whenever possible. Brain tissue is examined by routine histologic stains (hematoxylin and eosin, Congo red) as well as immunostaining for amyloid beta protein or other amyloid proteins as indicated. In a study in which biopsy was simulated on postmortem brains with known cerebral amyloid angiopathy severity, the identification by Congo red staining of any degree of vascular amyloid in the biopsy specimen was highly sensitive for the diagnosis of definite cerebral amyloid angiopathy. The specificity for this diagnosis increased with greater severities of cerebral amyloid angiopathy in the biopsy specimen (Greenberg and Vonsattel 1997).

Data raise the possibility that cerebrospinal fluid markers may have an ancillary role in the diagnostic evaluation of cerebral amyloid angiopathy. In Alzheimer disease, analysis of cerebrospinal fluid has found Aß42 concentration to be lowered and concentration of the microtubule-associated protein tau to be elevated (Clark et al. 2003). Analysis of cerebrospinal fluid in 17 nondemented individuals with probable cerebral amyloid angiopathy found a slightly different formula: reduced concentrations of both Aß42 and Aß40 with normal or mildly increased tau (Verbeek et al. 2009). Cerebrospinal fluid assays for Aß42 and tau are commercially available and may be considered when seeking confirmation of cerebral amyloid angiopathy.

The only definite use for genetic testing in cerebral amyloid angiopathy is to identify mutations associated with 1 of the hereditary syndromes. Despite apolipoprotein E’s role as a risk factor for the presence and progression of cerebral amyloid angiopathy, the results of apolipoprotein E genotyping do not appear to be either sensitive or specific enough to change current medical decision-making.

Cerebral amyloid angiopathy-related inflammation is associated with a distinct set of diagnostic findings. In addition to its defining neuropathologic appearance, this syndrome is also characterized by the striking MRI finding of T2-weighted hyperintensities, often asymmetric, involving periventricular and subcortical white matter and sometimes reaching the overlying cerebral cortex. Multiple lobar microbleeds are often present on gradient-echo sequences, not necessarily restricted to the cortical lobes affected by the T2 hyperintensities. Typically, little or no gadolinium enhancement is seen, with no diagnostic finding on MR-, CT-, or catheter-based angiography, presumably reflecting the very small size of the inflamed vessels. An intriguing, though still unexplained, association has been noted between cerebral amyloid angiopathy-related inflammation and the apolipoprotein E4/E4 genotype (Kinnecom et al. 2007).

Management of acute lobar hemorrhage due to cerebral amyloid angiopathy is similar to hemorrhages of other etiologies. Although early surgical removal of supratentorial intracerebral hemorrhages has not been found beneficial, the trial data are consistent with the possibility that evacuation may benefit patients with the lobar or superficial hemorrhages most commonly encountered in cerebral amyloid angiopathy (Mendelow et al. 2005; Mendelow et al. 2013). Despite concerns that brain surgery might be especially hazardous in cerebral amyloid angiopathy because of an increased risk of perioperative bleeding, published series indicate that resections can be performed without elevated postoperative risk (Minakawa et al. 1995; Izumiwara et al. 1999; Zhang et al. 2012). Current medical management for acute intracerebral hemorrhage includes blood pressure control, supportive medical care, discontinuation of antiplatelet agents, and reversal of anticoagulation. Osmotic agents and hyperventilation may be employed for temporary amelioration of raised intracranial pressure.
Currently, no active treatments for prevention of hemorrhage recurrence in cerebral amyloid angiopathy have been definitively established. However, some measures can reasonably be taken. Careful control of hypertension appears to be a prudent course in patients with cerebral amyloid angiopathy. This approach is supported by a secondary analysis of the Perindopril Protection against Recurrent Stroke Study (PROGRESS), in which stroke patients randomized to treatment with perindopril plus optional indapamide demonstrated lower risk of any intracerebral hemorrhage (50% risk reduction, 95% CI 26% to 67%) as well as specifically lower risk of intracerebral hemorrhages meeting criteria for probable cerebral amyloid angiopathy (77% risk reduction, 95% CI 19% to 93%) (Arima et al 2010). As focal seizures may be a relatively common clinical manifestation of cerebral amyloid angiopathy, use of antiepileptic agents in patients with suspected cerebral amyloid angiopathy and recurrent stereotyped events is worth trying. Sodium valproate is not a preferred anticonvulsant because of potential effects on platelet function. It remains unclear whether a net benefit exists to starting anticonvulsants before a seizure occurs.

Anticoagulation increases both the likelihood and severity of hemorrhagic stroke and in general should be avoided in patients with cerebral amyloid angiopathy-related hemorrhage. Although data from controlled trials are lacking, a decision-analysis model suggested that for patients with cerebral amyloid angiopathy-related hemorrhage, the increased risk of catastrophic recurrent hemorrhage associated with anticoagulation outweighs the beneficial effects of preventing atrial fibrillation-related thromboembolic stroke (Eckman et al 2003). Antiplatelet agents also increase the risk of hemorrhage, but the effect is substantially smaller. Therefore, it is reasonable practice to consider antiplatelet treatment for certain definite indications such as prevention of myocardial infarction, and otherwise to withhold them from patients with cerebral amyloid angiopathy-related hemorrhage. The risk of antiplatelet and anticoagulant therapy may be increased in the presence of an apolipoprotein E2 allele (McCarron et al 1999b; Rosand et al 2000). Similar questions have been raised about use of statin medications, which appear to increase the risk of hemorrhagic stroke (while decreasing the overall risk of stroke) when used for secondary stroke prevention (Amarenco et al 2006; Goldstein 2008). Prudent practice in treating patients with cerebral amyloid angiopathy would be to use statins when clearly indicated for prevention of myocardial infarction or ischemic stroke but to withhold them in the absence of a definite indication.

Although immunosuppressive therapy has no established role for non-inflammatory cerebral amyloid angiopathy, it appears to cause clinical and radiologic improvement in the majority of patients with the syndrome of cerebral amyloid angiopathy-related inflammation. In a follow-up study of 12 patients with cerebral amyloid angiopathy-related perivascular inflammation, 10 patients had initial improvement to immunosuppression but 3 of those 10 had subsequent relapse of symptoms, whereas the remaining 2 patients showed no response. The volume of T2 hyperintensities generally paralleled clinical improvements and subsequent relapses, making MRI a reasonable marker of treatment effect (Neuropathology Group 2001).

Reasonable choices for immunosuppressive regimen are a 5-day course of high-dose corticosteroids (500 mg-1 g/day x 5 days) as an inpatient or outpatient with rapid steroid taper. If there is no radiographic and/or clinical change, cyclophosphamide (1-2 mg/kg/day PO for 2 weeks) could be considered (consideration of brain biopsy to confirm diagnosis prior to initiating treatment is recommended). Other immunosuppressive agents may be further alternatives in high refractory cases, although clinical experience with these agents remains very limited. The treating clinician may also wish to consider the following if appropriate: ensuring adequate calcium (1200-1500 mg/day), and vitamin D (400-800 units/day), yearly bone density measurements, and vitamin D level checks every 6 months (supplement if below 30 ng/ml).

The future prospects for developing disease-modifying treatments for cerebral amyloid angiopathy appear good. Cerebral amyloid angiopathy has a defined set of steps in its pathogenesis, including amyloid beta protein production, aggregation, clearance, and cellular toxicity, each of which serves as a potential target for drug therapy. Given improvements in identifying the presence and progression of cerebral amyloid angiopathy and the high volume of investigations into treatment approaches for amyloid beta protein-related disease, future years are likely to see multiple trials of biologically plausible candidate agents aimed at slowing this currently untreatable form of cerebrovascular disorder.

Massachusetts General Hospital has participated in “Study Evaluating the Safety, Tolerability and Efficacy of PF-04360365 in Adults with Probable Cerebral Amyloid Angiopathy”, Pfizer, ClinicalTrials.gov identifier: NCT01821118.
**Special considerations**

**Pregnancy**

No evidence indicates increased risk in pregnancy in patients with cerebral amyloid angiopathy. Except in some familial forms, most patients will be beyond childbearing years.

**Anesthesia**

No evidence exists to show increased risk from anesthesia in patients with cerebral amyloid angiopathy.

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**References especially recommended by the author or editor for general reading.**

**Former authors**

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**ICD and OMIM codes**

**ICD codes**

ICD-9:
- Intracerebral hemorrhage: 431
- Cerebral infarction: 436
- Transient ischemic attack: 435

ICD-10:
- Intracerebral haemorrhage, unspecified: I61.9
- Stroke, not specified as haemorrhage or infarction: I64
- Transient cerebral ischaemic attacks and related syndromes: G45

**OMIM numbers**

- Hereditary cerebral hemorrhage with amyloidosis—Icelandic type: #105150
- Hereditary cerebral hemorrhage with amyloidosis—Dutch type: #605714
- Hereditary cerebral hemorrhage with amyloidosis—Flemish type: #605714
- Oculocephaloleptomeningeal amyloidosis: #105210
- Amyloid beta A4 precursor protein: *104760

**Profile**

**Age range of presentation**

- 45-64 years
- 65+ years

**Sex preponderance**

- male=female

**Family history**

- family history may be obtained

**Heredity**

- heredity may be a factor
- autosomal dominant

**Population groups selectively affected**

- Dutch
- English
- Flemish
- Hungarians
- Icelanders
- Japanese

**Occupation groups selectively affected**
none selectively affected

**Differential diagnosis list**

- malignant hypertension
- hypertensive hemorrhage
- arteriovenous malformations
- cavernous hemangiomas
- hemorrhage into cerebral neoplasms
- trauma
- vasculitis
- coagulopathies
- mycotic aneurysms
- cerebral venous thrombosis
- hypertensive vasculopathy
- diffuse arteriosclerosis
- cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Fabry disease
- moyamoya disease
- fibromuscular dysplasia

**Associated disorders**

- Alzheimer disease
- Arteriovenous malformations
- Cerebral infarction
- Dementia
- Dementia pugilistica
- Demyelinating diseases
- Diffuse Lewy body disease
- Down syndrome
- Intracerebral hemorrhage
- Leukoaraiosis
- Lobar hemorrhage
- Malignant neoplasms and radiation necrosis
- Prion disease
- Seizures
- Transient ischemic attacks
- Vasculitides

**Other topics to consider**

- Alzheimer disease
- Blood-brain barrier
- Brainstem hemorrhage
- Down syndrome
- Lobar hemorrhage
- Nontraumatic intracerebral hemorrhage
- TIAs (carotid)
- Vertebrobasilar transient ischemic attacks

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