Cerebral Amyloid Angiopathy*

Serebral Amyloid Anjiyopati*

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ÖZET


Anahtar Kelimeler: Serebral amiloid anjiyopati, serebral kanama, kognitif bozukluk, manyetik rezonans görüntüleme.
ABSTRACT
Cerebral Amyloid Angiopathy
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Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of amyloid beta-peptides (Aβ) in the walls of leptomeningeal arteries, arterioles, and veins. Despite the fact that these pathological changes were first described in 1909, major advancement in our understanding of the clinicoradiological manifestations, neurobiology, and course of CAA has occurred only during the last 30 years. No significant associations have been shown between CAA and other systemic/visceral amyloidoses or vascular risk factors, including hypertension. CAA is well known as the most common cause of spontaneous and anticoagulant-related lobar parenchymal ICH in the elderly. It also causes lobar cerebral microbleeds (CMBs), small dot-like dark susceptibility artifacts visible with gradient recalled echo (GRE)-magnetic resonance imaging (MRI). CMBs are important markers of disease severity and predictors of CAA progression. Amyloid angiopathy is also a common cause of ischemic microvascular white matter disease (WMD) and deep cerebral infarctions. Such WMD is defined as subcortical and periventricular white matter changes without obvious infarction, as well as a dark appearance on computerized tomography (CT) and a bright appearance on fluid attenuated inversion recovery (FLAIR)-MRI.

CAA-related vascular dysfunction, with its hemorrhagic and ischemic complications, is a recognized contributor to vascular cognitive impairment in the elderly, an independent effect that is synergistically increased by Alzheimer pathologies, such as plaques and tangles. A set of clinicoradiological criteria was established for the accurate diagnosis of CAA. According to the Boston Criteria, patients aged 55 years and older with multiple hemorrhages (on CT or GRE-MRI) restricted to the lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) are diagnosed as probable CAA when no other etiology is found; a single hemorrhage in the same region is classified as possible CAA. Current guidelines recommend that patients with non-valvular atrial fibrillation suspected to have CAA-related ICH not be offered long-term anticoagulation therapy because of the significant risk of rebleeding.

Key Words: Cerebral amyloid angiopathy, cerebral hemorrhage, cognitive impairment, magnetic resonance imaging.
rebral parenchymal and vascular amyloid deposits—albeit closely related—are different. In CAA, amyloid infiltrates the media and adventitia of small- to medium-sized leptomeningeal and superficial cortical vessels, resulting in effacement of the vessel wall, sometimes to the point that its identification as arterial or venous is impossible. Affected vessels might show a distinctive “double-barrel” appearance. These vessels might undergo fibrinoid degeneration or necrosis, as well as segmental dilation with microaneurysm formation, leading to vessel rupture and hemorrhage. No significant relationship between CAA and other systemic/visceral amyloidoses has been reported.

The sequence of events that triggers the deposition of cerebrovascular amyloid, the determinants of its distribution and progression, and the mechanisms of blood vessel injury are not well understood. More than 10 different amyloid peptides are known to accumulate in cerebral parenchyma and vessels, but Aβ-related CAA is the most common form observed in AD and CAA (7); therefore, Aβ is thought to be detrimental to vessel structure and function. Aβ is generated by the sequential proteolytic processing of a transmembrane protein-amyloid β precursor protein (APP); the enzymes involved are β-secretase (BACE) and the γ-secretase/presenilin complex (8). Based on animal models, vascular amyloid appears most likely to be of neuronal origin, but the hematogenous and vessel wall hypotheses cannot be completely refuted (9).

Some genetic factors have been associated with early onset and familial types of CAA. A number of mutations located within the Aβ sequence or at the β- and γ-secretase cleavage sites can cause familial Aβ-CAA, such as the Dutch, Iowa, Italian, and Arctic types, or familial AD with prominent Aβ-CAA pathology (10). Even in the exceedingly more common form-sporadic CAA with clinical presentation 20 years later than in hereditary forms—a signifcant association between the presence of the APOE epsilon 2 (ε2) or epsilon 4 (ε4) alleles and greater risk of CAA-related hemorrhage was observed when compared to people that had only the common APOE epsilon 3 (ε3) allele (11,12). The APOE ε4 allele has been associated with increased Aβ deposition, whereas APOE ε2 is associated with vessel pathology, such as cracking and necrosis that predispose to rupture; these associations further support a mechanistic link between APOE ε allele carrier status and vessel pathology in CAA (13,14). Regarding the accumulation of Aβ in vessel walls, both increased production and decreased degradation have been proposed as potential culprits.

Currently, observations from transgenic mice models support the hypothesis that impaired interstitial fluid drainage results in decreased Aβ clearance, thereby promoting Aβ aggregation and vascular deposition. A detailed discussion of the proposed mechanisms of Aβ-related vascular injury is beyond the scope of this review, but the aforementioned genetic factors in combination with acquired factors, such as age-related degenerative changes, minor trauma, and focal amyloid accumulation, appear to promote vascular toxicity of the Aβ, triggering the pathological cascade that ultimately results in the clinical manifestations of CAA.

Autopsy series report a propensity for severe CAA pathology to involve the parieto-occipital regions (5). These data are supported by advanced radiological studies that report more lobar bleeds and significant retention of an in vivo amyloid-labeling agent (Pittsburgh Compound B) in the posterior regions of the brains of patients with CAA (15,16).

**Epidemiology**

Inconsistencies in the definition of CAA in postmortem pathologic case series make it difficult to compare its prevalence across studies, but there is unequivocal evidence showing that both the prevalence of CAA pathology and the incidence of its clinical manifestations increase with age. In a large autopsy series consisting of 784 consecutive postmortem brain pathology studies, the prevalence of moderate to severe CAA was 2.3% among patients aged 65-74 years, 8% among those 75-84 years, and 12.1% among those over 85 years (17). In a series of 400 consecutive autopsies from Japan, CAA of any grade was observed in at least one section in 91 cases (22.8%) and was strongly correlated with age. The presence of CAA did not correlate with blood pressure nor with the severity of cerebral atherosclerosis, a finding replicated in most subsequent studies (18). Another study that compared the frequency of CAA pathology in AD patients and age-matched controls reported a significantly higher rate in AD patients (94.1% vs. 33.3%) (19).

Figure 1. Aβ immunohistochemistry shows the replacement of many arteriolar walls by Aβ-immunoreactive material.

![Figure 1](image-url)
CLINICORADIOLOGICAL FEATURES and DIAGNOSTIC CRITERIA

Lobar Intracerebral Hemorrhage (ICH)

Spontaneous cortical and corticosubcortical (lobar) ICH is the clinical hallmark and a dreaded consequence of CAA. CAA is also an important cause of warfarin-associated lobar ICH in the elderly (20). The worldwide annual incidence of primary ICH is 30-52/100,000 (21,22). Recent population-based studies showed an increase in antithrombotic-associated bleeds and lobar hemorrhages, possibly related to CAA in the aging population-further evidence of the importance of CAA as a public health problem (23,24). The annual age- and sex-adjusted lobar ICH incidence rate was 9.0/100,000, yielding a deep to lobar ratio of 2.3:1, but it should be remembered that other rare etiologies such as vascular malformation might also cause lobar ICH (22). Advanced age, again, represents the strongest risk factor for CAA-related ICH, whereas gender does not appear to play a significant role. In a clinicopathologic series of 107 patients with sporadic CAA-related ICH (mean age: 72 years) compiled by Vinters, the frequency of high blood pressure was 31.8% (5). This rate is low compared to the > 50% prevalence of hypertension among Americans aged 65 years and older, and hypertension has not been shown to be a significant risk factor for CAA-related ICH (25).

APOE ε4 and ε2 allele carrier status as a risk factor for increased vascular Aβ accumulation and for vessel pathology resulting in rupture were discussed in the Pathophysiology section (13,14). The APOE ε2 allele was overrepresented among patients with warfarin-associated lobar hemorrhage and there is strong evidence suggesting that CAA is an important cause of anticoagulant-related lobar ICH in the elderly (20). The recognition of this association and the high rate of ICH recurrence in CAA have led to a change in recommendations regarding long-term anticoagulation as a secondary prevention strategy (26). While antiplatelets can be resumed in survivors of both deep and lobar ICH without a major increase in the risk of recurrent bleeds, it is recommended that survivors of suspected CAA-related ICH with non-valvular atrial fibrillation not be offered long-term anticoagulation (27,28). Current guidelines do not recommend routine genetic testing or MRI screening in an attempt to identify asymptomatic CAA before starting long-term anticoagulation therapy (29).

CAA-related hemorrhages are located in the cortical and corticosubcortical regions of the brain, which are also the most common sites of vascular amyloid deposition. A gradient-echo MRI-based study of 59 patients with probable CAA reported that hemorrhages are more likely to occur in the temporal and occipital lobes, and that they tend to recur in areas of prior hemorrhage, regardless of lobe, suggesting that regional differences within the brain play a role in the development of CAA-related hemorrhages. The cerebellum might contain some vascular amyloid and was reported to occasionally show CAA-related ICH. The pons is not a site associated with CAA-related ICH and it is critically important to remember that deep seated hematomas—whether in the basal ganglia/thalamus or in brainstem—are typically not associated with CAA pathology (30).

Clinically, acute CAA-related lobar ICH is not significantly different than other types of ICH. The size and location of the bleed, together with the clinical severity in the acute phase, determine the outcome. Any anticoagulation should be rapidly reversed and other aspects of ancillary care should be provided according to current guidelines (31). Cerebellar hemorrhages should be treated, with particular attention to the mass effect and impending risk of ventricular outflow obstruction, and increased intracranial pressure that might result in herniation unless treated with decompressive surgery (32). Based on the existing data, small differences between lobar and deep ICH might exist in terms of clinical course and treatment response. Patients with a small lobar ICH might be at greater risk of immediate seizure and their bleeds are more likely to extend into the subarachnoid space than into the ventricles (33). Despite the fact that early surgical intervention did not show any significant benefit in ICH patients overall, a meta-analysis of 293 patients with lobar hemorrhage included in 3 randomized trials suggest that a better outcome is obtained with early surgery in lobar ICH cases (34). The Surgical Trial in Intracerebral Hemorrhage II (STICH II) is currently underway in an effort to compare the benefit of surgery within 48 hours to initial conservative management in patients with spontaneous ICH located within 1 cm of the cortical surface. If this ongoing study confirms the beneficial effect reported in the meta-analysis, surgical evacuation might become an important acute treatment option for CAA-related lobar ICH patients (34).

The course of the disease is characterized by recurrent lobar hemorrhages, with a 2-year cumulative recurrence rate of 21% in a cohort of 71 consecutive survivors of lobar ICH (35). Molecules that can interfere with the pathogenic Aβ cascade have been tested in preliminary studies, but currently there is no treatment that can halt the progression of the pathology or its clinical course.

Rare Clinical Manifestations

Transient neurological symptoms constitute a rare, but known entity in CAA. Such patients describe spells consisting of negative (weakness, numbness) or positive (paresthesias) symptoms of short (seconds-to-minutes) duration that can spread smoothly over contiguous body
parts (36). These episodes are thought to originate from epileptic activity or spreading depression of the cortex surrounding small hemorrhages. As these spells are mostly recurrent and stereotypical, transient ischemic attacks should be a part of the differential diagnosis and these patients should undergo vascular imaging to rule out proximal vessel stenosis. Performing and carefully reviewing GRE-MRI is important for identifying a corresponding superficial bleed in order to avoid antithrombotic treatments that might be hazardous in the presence of CAA.

A number of case reports describe patients that presented with subacute cognitive/behavioral changes, seizures, headache, and focal neurological deficits. These patients also had significant white matter hyperintensities (WMH) on T2-weighted MRI and cerebrospinal fluid exams, indicating ongoing inflammation in the absence of infection. Two closely related categories, both associated with severe CAA pathology, were identified upon neuropathologic evaluation:

1. Aβ-related angiitis that often shows granulomatous, angiodestructive inflammation and meningeal lymphocytosis (37), and

2. CAA-related perivascular inflammation with multinucleated giant cells, but no angiographic or pathologic evidence of vasculitis (38). The recognition of these clinicopathological entities is important, as they might respond favorably to immunosuppressive treatment.

### Radiological Features and Diagnostic Criteria

Brain CT is fast, widely available, and accurate in the early diagnosis of ICH. Nevertheless, MRI outperformed CT in emergency assessment of patients with most types of suspected acute strokes, and both modalities performed similarly in the detection of acute intracranial hemorrhage (39). GRE-MRI revolutionized clinical practice and research involving CAA patients by virtue of its ability to show both acute (deoxyhemoglobin-containing) and old (hemosiderin-containing) bleeds as strong hypointense areas. GRE sequences are ideal for demonstrating microbleeds that may not be seen with other imaging studies. CMBs are small dot-like hypointense lesions ≤ 5 mm in diameter that represent hemosiderin deposition from tiny (mostly subclinical) blood leaks (Figure 2A). A detailed field guide for accurate detection and interpretation of CMBs was recently published (40). Furthermore, the Stroke Diagnostics and Therapeutics Branch of the National Institute of Neurological Disorders and Stroke has an interactive website dedicated to the interpretation of GRE-MRI in acute stroke patients, and includes examples of hemorrhage mimics and other GRE findings, as well as self-assessment tools (http://gre.ninds.nih.gov/). CMBs proved to be an important predictor of clinical and radiological deterioration in CAA patients. Microhemorrhages are common in patients with CAA-related symptomatic ICH and their lobar distribution is similar to that of macrobleeds. Greater number of hemorrhages at baseline is predictive of an increased risk of subsequent cognitive impairment, loss of independence, or death among patients not previously demented/dependent, as well as the risk of future symptomatic ICH (26).

One of the key achievements in CAA research has been the development and validation of a set of criteria that allows this diagnosis to be made in living patients (4). According to the Boston Criteria, patients aged 55 years and older with multiple hemorrhages (on CT or MRI-GRE) restricted to the lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) are diagnosed as probable CAA when no other etiology is found; a single hemorrhage in the same setting is classified as possible CAA (4). The criteria do not specifically state the minimum imaging requirements to exclude other underlying pathologies (i.e., vascular malformations, tumor, hemorrhagic infarction), but most lobar ICH patients in the United States undergo brain MRI that includes GRE, diffusion-weighted, and post contrast T1-weighted sequences. If ≥ 2 micro- or macrobleeds are found in a patient over 65 years, without clinical or radiological suspicion of an alternative etiology, the diagnosis of probable CAA is generally made. Among younger patients, in those with single lobar bleeds and in all patients that raise suspicion of a different underlying pathology, further imaging and diagnostic testing is performed. Advanced testing is tailored according to the individual patient’s presentation and might include non-invasive imaging, such as MR angiography or CT angiography, or invasive tests, such as cerebral angiography, lumbar puncture, and in rare cases a brain biopsy. A clinicopathological correlation study was performed with 39 patients that had a clinical diagnosis of probable or possible CAA and full postmortem pathological assessment (4). All 13 patients diagnosed with probable CAA according to Boston Criteria had significant amyloid angiopathy on pathological evaluation, indicating a very high specificity of the probable category. Among the 26 patients with the diagnosis of possible CAA, 16 (61%) were pathologically confirmed as having severe CAA, suggesting a fair specificity for this category (4). Boston Criteria has made it possible to enroll well-characterized CAA patient populations into clinical studies, thereby facilitating advances in our understanding of the clinical, radiological, and physiopathological correlates, as well as the course of this condition in humans.

### Amyloid Angiopathy-Related Vascular Dysfunction and Ischemic Manifestations

An association between hereditary CAA and cognitive impairment has been reported in the few familial forms of CAA (41). Clinical observations suggesting such an associ-
ation between the much more common sporadic forms of CAA and cognitive impairment also exist, but have only recently been tested in prospectively identified cohorts that underwent standardized cognitive testing and imaging studies. Advances in MR imaging and analysis methods have also made it possible to investigate the association between CAA and WMD that appears in subcortical and periventricular brain regions as bright lesions with T2/FLAIR MRI sequences (Figure 2B,2C).

Two population-based autopsy series suggested that the presence of CAA pathology might be independently associated with the risk of dementia, even after adjusting for age and markers of concomitant AD pathology, such as plaque and tangle counts (42,43). These studies included unselected community-dwelling elderly individuals with a mean age at death of 85 years. The presence of hemorrhages did not account for the increased risk of dementia found in patients with CAA pathology, but only a few of them had brain bleeds. The potential factors that might mediate such a link might be the direct effects of critically located cerebral macro- or microhemorrhages, cortical or subcortical infarcts, and widespread WMD that result in disruption of neural tracts.

In a study that assessed the relationships between white matter lesions, cognitive impairment, and other clinical markers of disease severity in a CAA cohort, WMD was a frequent finding on brain imaging (found in 77%, severe in 32%). WMD was associated with GRE-MRI hemorrhage counts and with the risk of recurrent ICH. Patients with cognitive impairment prior to their index ICH were more likely to have severe WMD on CT and advanced periventricular WMH on MRI, even after adjusting for age (44). The view that advanced CAA can induce clinically important vascular dysfunction that might ultimately result in white matter ischemia became an intriguing hypothesis for the association between CAA, WMD, and cognitive impairment, and fueled further clinical and laboratory research (45).

Using sensitive quantitative methods to measure white matter hyperintensities (WMH), we have found that CAA patients had almost twice the WMH volume that AD patients and individuals with mild cognitive impairment (MCI) had (1). This association is even more striking in view of the data showing increased WMD in AD patients when compared to non-demented age-matched controls, which suggests that CAA pathology may contribute independently to ischemic changes in white matter (46). Our group also noted an average 18% annual increase in WMH volume in CAA patients and that there was an independent association between the rate of progression and the presence of cognitive impairment (47). The anatomic distribution of WMD in patients with advanced CAA was compared to that of healthy controls using diffusion tensor imaging (DTI). Fractional anisotropy (FA), calculated from DTI, is a measure of the directional diffusivity of water, and it is thought to represent white matter integrity. FA was reduced in CAA, specifically in temporal white matter and in the splenium of the corpus callosum, suggesting that advanced CAA could be associated with a characteristic pattern of regional brain tissue degeneration (48). Another very recent study identified small areas of restricted diffusion (acute silent infarcts) in
12 of 78 subjects (15%) with CAA versus 0 of 55 AD/MCI subjects, further supporting the view that CAA causes ischemic lesions in addition to ICH (49).

Several studies directly addressed the unexplained issue of the mechanism of vascular dysfunction in CAA. Plasma Aβ40 concentration (but not Aβ42 level) was found to be independently associated with WMH volume in individuals with CAA, AD, and MCI (1). Aβ40 peptide is the soluble form most commonly found in vessel walls, whereas Aβ42 is primarily observed in parenchymal plaques in AD. In a transgenic mouse model Aβ40 (but not Aβ42) applied to the mouse cortex blunted the physiological increase in cerebral blood flow that normally results from pharmacological (acetylcholine, bradykinin, or calcium ionophore) and physiological (sensory stimulation) stimuli (50,51). Accumulation of Aβ40 deposits in the walls of leptomeningeal vessels in CAA patients might result in ischemia in the territory of the distal end arteries running to the deep white matter, presumably via similar mechanisms. A recent study used transcranial Doppler ultrasound to compare cerebral vascular reactivity (VR) in patients with CAA to healthy age-matched controls. Patients with CAA showed significantly decreased VR in the posterior cerebral arteries in response to visual stimulation, possibly reflecting an occipital predilection of the pathology (52). In summary, there is now ample data from both human and animal studies that support the theory that CAA-induced vascular dysfunction is a cause of ischemic microvascular white matter damage in the elderly. CAA and CAA-related WMD appear to contribute independently to cognitive impairment in the elderly, giving CAA a high priority in dementia as well as in stroke research.

THE FUTURE

One of the limitations of studying Aβ in humans, until recently, has been the lack of in vivo markers of Aβ; therefore, quantitative studies have had to rely on autopsies. The development of positron emission tomography (PET) ligands that can bind to Aβ deposits has revolutionized research in CAA and AD. Pittsburgh compound B (PiB) is one of these molecules, a derivative of Congo red with a carbon 11 atom attached. The binding is increased most prominently in the frontal cortex in AD and the occipital cortex in CAA (16,53). PiB-PET detection of vascular Aβ can serve as a method for identifying the location and extent of CAA in living subjects. PiB might become an invaluable marker of disease severity, disease progression, and treatment response if ongoing studies prove its correlation with these measures. In a 42-year-old man with subtle clinical signs of Iowa-type hereditary CAA, we observed elevated PiB retention, selectively in the occipital cortex, sparing regions typically labeled in AD (54). This finding strongly suggests that PiB-PET can non-invasively detect isolated CAA prior to overt signs of hemorrhagic/ischemic brain damage and can potentially help in the identification and stratification of pre-symptomatic patients for enrollment in clinical studies.

Recent studies using in vivo kinetic measurements via multiphoton imaging in transgenic mouse models provided some insight into the initial vessel involvement and propagation of CAA. The earliest appearance of CAA was observed in leptomeningeal arteries as multifocal deposits of band-like Aβ. Over subsequent imaging sessions, these deposits grew locally and new foci appeared in different segments (additional initiation events). During the early phases of CAA development, the overall pathology burden progressed at a consistent rate, raising hopes that this model is amenable to investigations of therapeutic interventions (55).

CONCLUSIONS

Following rather slow but constant progress in the understanding of CAA during the 7 decades following its initial description, there has been a huge increase in research into its cause, genetic associations, disease mechanisms, clinical manifestations, and natural course. We now have a validated set of clinicoradiological criteria that allows accurate diagnosis of CAA in living patients. CAA is well established as the most common cause of lobar parenchymal macro- and microbleeds in the elderly, but also as a common cause of ischemic microvascular white matter injury and deep cerebral infarctions. CAA-related vascular dysfunction, with its hemorrhagic and ischemic complications, is a recognized cause and/or contributor to vascular cognitive impairment in the elderly, an independent effect that is synergistically increased by Alzheimer pathologies, such as plaques and tangles. There is currently no treatment that is proven to stop the progression of CAA, but research has shown a number of relevant therapeutic targets as well as new radiological markers of disease severity and progression that will be useful when potential treatments are ready to be tested in clinical trials.

REFERENCES


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