

Intracerebral hemorrhage

Cerebral Amyloid Angiopathy – A Disease or Age-Related Condition

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Abstract

Cerebral amyloid angiopathy is characterized by deposition of amyloid in the walls of leptomeningeal and cerebral blood vessels. Its most common form, sporadic CAA that results from deposition of β -amyloid peptide, which is the subject of this short review, is present in virtually all cases of Alzheimer disease and is also common among non-demented subjects where its prevalence increases with age. Stroke due to massive cerebral lobar hemorrhage is the main clinical presentation of CAA, but transient neurologic symptoms due to microhemorrhages may also occur. CAA is also a risk factor for cerebral infarction and there is increasing evidence that CAA contributes to cognitive impairment in the elderly, usually in association with white matter abnormalities on imaging. Although the definitive diagnosis of CAA is neuropathologic, reliable diagnosis can be reached clinically, based on the occurrence of strictly lobar hemorrhages, particularly in the cortico-subcortical area when using gradient-echo or T2*-weighted magnetic resonance imaging. Experimental studies have shown that the origin of the vascular amyloid is neuronal, and that age-related degenerative changes in the vessel walls prevent its clearance from the brain along perivascular spaces and promote A β aggregation and CAA formation. The entrapped A β aggregates are toxic to various vascular wall components, including smooth muscle cells, pericytes and endothelial cells, leading to their eventual destruction and predisposition of the vessel wall to rupture and hemorrhage. However, more research is necessary to decipher the mechanism of CAA formation and its relation to cognitive decline in the elderly.

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Cerebral amyloid angiopathy is a disorder characterized by deposition of amyloid in the walls of leptomeningeal and cerebral blood vessels. Amyloid is a pathologic proteinaceous substance, the end product of a protein misfolding disorder that results in aggregation and subsequent formation of highly insoluble fibrils rich in β -pleated sheet conformation [1]. Despite the fact that all amyloid deposits have a uniform appearance and are made up largely of non-branching fibrils of approximately 7.5–10 nm in width ultrastructurally, it is clear that amyloid is not a chemically distinct entity. There are 26 known proteins or their proteolytic products which form subunits that assemble into amyloid fibrils, but only 8 of them deposit in the brain [2]. A proportion of CAA occurs in a number of familial hereditary conditions [1,2],

but only the most common sporadic form of CAA, which results from deposition of the β -amyloid peptide, is the subject of this short review.

Historical note

The deposition of amyloid in the walls of cerebral blood vessels was first described by Scholz in 1938 in the brains of elderly individuals [3]. It was subsequently noticed that CAA is a common feature of Alzheimer disease [4]. The interest in CAA was significantly increased in the 1970s when it was recognized that CAA is a common cause of intracerebral hemorrhage in elderly non-hypertensive people [5]. In recent years, following the impressive advances in the prevention and treatment of stroke caused by disease of the large arteries, there is a renewed interest in CAA (and in other small vessel diseases) due to the potential role of CAA in the pathogenesis of ICH and its relation to cognitive impairment in old age [6,7].

Pathology

Amyloid deposition most frequently affects leptomeningeal and cortical small and medium-sized arteries and arterioles (and less commonly capillaries and veins) in the form of hyaline, amorphous, eosinophilic thickening of their walls [5]. Blood vessels in the white matter and in other regions of the brain are not affected to any significant degree [8]. Amyloid initially tends to deposit around smooth muscle cells in the abluminal portion of the tunica media and adventia (mild form of CAA according to Vonsattel et al. [9]). This is followed by progressive destruction of smooth muscle cells (moderate form of CAA) and, subsequently, by degenerative changes such as disruption of the vessel's architecture with hyaline degeneration, "double-barreling," foci of fragmentation of the walls, microaneurysm formation and fibrinoid necrosis with evidence of perivascular leakage of blood (severe form of CAA) [5,9,10]. These changes can lead to severe luminal compromise with reduced perfusion and resultant ischemia and infarcts on the one hand, or reduced compliance, rupture and hemorrhage on the other.

As with all other forms of amyloidosis, the amyloid in the affected blood vessels displays apple-green birefringence when stained with Congo red and viewed with polarized light [Figure 1].

CAA = cerebral amyloid angiopathy

A β = β -amyloid peptide

ICH = intracerebral hemorrhage

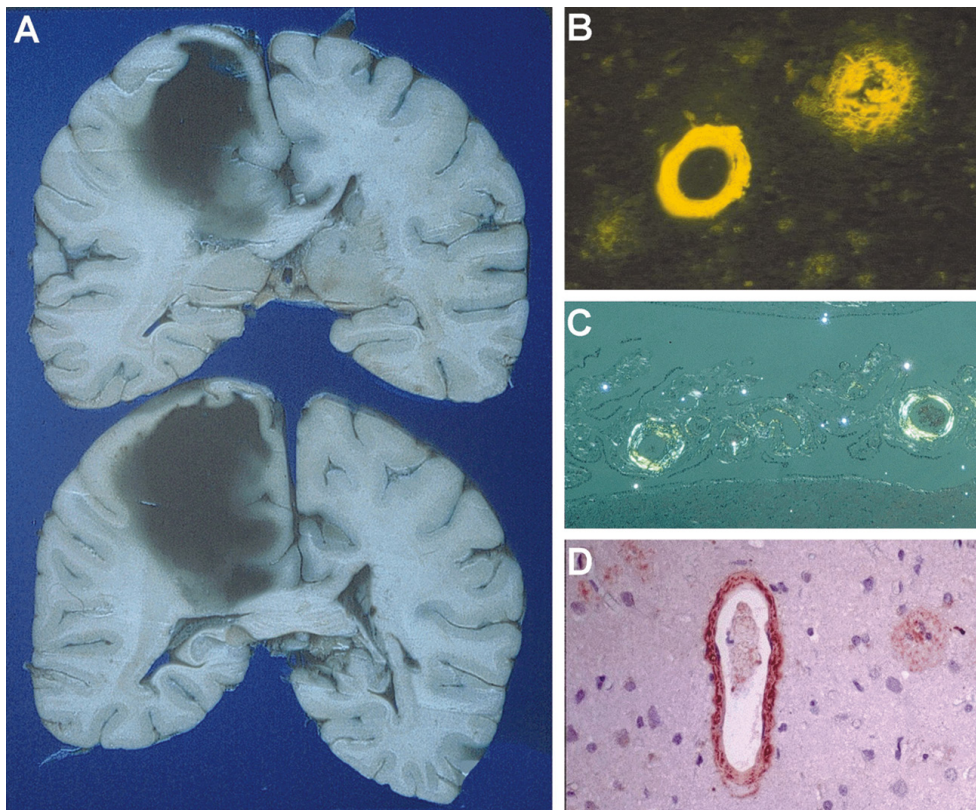


Figure 1. Pathologic features of CAA. **[A]** Lobar cerebral hemorrhage due to CAA. **[B-D]** Amyloid deposition in the wall of cerebral blood vessels. In **[B]** and **[D]** amyloid cores of neuritic (senile) plaques are also stained. B = thioflavin stain, C = Congo red, viewed with polarized light, D = A β immunostain.

Likewise, it is also stained with thioflavin and like all amyloids is made up of interwoven bundles of 7.5–10 nm straight filaments, ultrastructurally. A β deposits in CAA can be demonstrated immunohistochemically [Figure 1].

Prevalence, distribution and clinical presentation

CAA is present to some degree in virtually all cases of Alzheimer disease and Down's syndrome [9,11-13] and is also common in non-demented subjects. The prevalence of CAA in the general elderly population is approximately 10–40% [13-15] and increases with age. Thus, the prevalence of advanced CAA (graded as moderate or severe) was estimated to be 2.3% in 65 to 74 year olds, 8% in 75 to 84 year olds, and 12.1% in those over 85 [16].

Spontaneous ICH is the main clinical manifestation of CAA that otherwise usually remains clinically silent. ICH accounts for approximately 12% of all strokes [17], and CAA is the second most common cause of ICH, responsible for approximately 10–20% of all ICH in the elderly [16]. In contrast to the much more common hypertensive ICH, CAA-related lobar hemorrhages affect the more superficial parts of the cerebral hemispheres, i.e., cortex and subcortical white matter, and are often recurrent. CAA-related ICH can present with sudden onset of typical stroke-like symptoms, or with transient neurologic symptoms due to microbleeds [18], which are often misdiagnosed [19]. Recent

studies have shown that CAA is also a risk factor for cerebral infarction [20] and that CAA is significantly more common in patients with infarction than age-matched controls with non-vascular lesions [21].

Another clinical presentation of CAA concerns cognitive impairment. It has long been noted that CAA is primarily associated with Alzheimer's disease. In addition, there were reports of individual instances of dementia in association with CAA, usually with concomitant association of white matter disease [7,15,18,22]. Recent population-based studies indicate that CAA contributes to cognitive decline in elderly individuals without Alzheimer's disease [13,15,23].

A small subset of patients with CAA who have CAA-related vasculitis or perivascular inflammation present with relatively rapid cognitive decline, headaches, seizures, focal neurologic deficit and prominent white

matter abnormalities on imaging, which usually respond to immunosuppressive therapy [12,24-26].

Much progress has been made in the diagnosis of CAA *in vivo*. Although neuropathologic examination (of brain biopsies or surgical resections removed during evacuation of hematomas) remains the definitive diagnostic approach to CAA, a reliable diagnosis (of "probable CAA") can be reached from clinical and radiographic data [27,28]. The occurrence of multiple strictly lobar micro- or macrohemorrhages, particularly microbleeds exclusively located in the cortico-subcortical area, on gradient-echo or T2*-weighted magnetic resonance imaging sequences form the basis for the clinical diagnosis. In addition, radiographically demonstrated microhemorrhages also predict both the risk of recurrent lobar ICH and future clinical decline [29]. Radiographic evidence of advanced white matter disease is also common.

There are somewhat conflicting data on the topographic distribution of the CAA-related hemorrhages in the brain. While some studies demonstrated preferential temporal and occipital lobe involvement [30], others have shown frontal or fronto-temporal predilection [9,31]. Generally, the regional severity of CAA correlated with the site of bleeding [9]. Controversy also arises concerning the use of anticoagulants and thrombolytic agents in patients with CAA [32]. Some investigators indicated that CAA may be a risk factor for thrombolysis-related ICH [33]

and that CAA is an important cause of warfarin-associated lobar ICH in the elderly [34]. Also, in a mouse model of CAA there was a significantly higher tendency for ICH after thrombolytic therapy compared with that of wild-type mice [35]. On the other hand, a recent extensive literature search concluded that there is currently no sufficient evidence for the notion that cerebral microhemorrhages increase the risk of ICH among patients on antithrombotic treatment or those treated with thrombolysis for acute stroke [28].

With regard to risk factors for CAA and CAA-related ICH, important are the E4 and the E2 alleles of apolipoprotein E, which are associated with younger age at onset of the first hemorrhage and shorter time till ICH [16].

Pathogenesis of CAA

The amyloid β peptide, which is deposited in the walls of cerebral and leptomeningeal blood vessels in CAA due to β -amyloid, is derived through sequential proteolytic process from a parent molecule – the amyloid β -protein precursor, which is a transmembrane protein. The majority of A β is 40 amino acid residues in length and this is the major form seen in A β -CAA [20,36]. A minor form containing 42 amino acid residues is also present, mainly in neuritic (senile) plaques of Alzheimer patients.

The pathogenesis of A β -CAA was recently reviewed by Herzig and colleagues [37]. There are various cellular and transgenic mouse models that have contributed greatly to our understanding of many aspects of the pathomechanism of the disease process. Analysis of these models has shown that the origin of vascular amyloid is mainly neuronal. Following its formation, A β is transported to the blood vessels along perivascular pathways along which interstitial fluid drains from the brain [38], or transported through the blood-brain barrier into the blood. Age-related changes of the vessel wall properties impair A β drainage, cause its entrapment and therefore promote A β aggregation and A β -CAA formation. Several studies have shown that the ratio of A β 40:42 is an important factor in determining whether A β accumulation occurs within the walls of cerebral blood vessels or in the brain parenchyma. The longer form of A β , A β (42), undergoes amyloid formation more rapidly than the shorter more soluble A β (40). Both forms, however, have emerged as potential mediators of cerebrovascular dysfunction. *In vitro* studies have shown that aggregates of A β are toxic to cultured human cerebrovascular endothelial cells and that soluble forms of A β assemble into fibril-like structures on the surfaces of human cerebrovascular smooth muscle cells and human brain pericytes that are influenced by apolipoprotein E genotype (reviewed by Herzig et al. [37]). Also, A β can influence vascular smooth muscle cell viability by altering adhesive interaction with the extracellular matrix [36]. These processes may lead to vascular fragility and predispose to rupture and hemorrhage.

More studies are needed in order to decipher the mechanism of A β -CAA and to understand its relation to cognitive decline in old age.

A β -CAA = CAA due to A β

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