Cerebral Amyloid Angiopathy
Progressive Disruption of the Neurovascular Unit

Gregory J. Zipfel, MD; Henry Han, PhD; Andria L. Ford, MD; Jin-Moo Lee, MD, PhD

Abstract—Cellular elements of the neurovascular unit are essential for the physiological functioning of brain vessels. If any of these vascular elements are disturbed the consequences can be dire. Cerebral amyloid angiopathy (CAA), a disorder caused by the accumulation of amyloid in cerebral vessels, provides a case study of progressive neurovascular unit dysfunction leading to failure of vascular reactivity, smooth muscle cell loss, and eventual frank breakdown of vessel integrity resulting in recurrent and sometimes fatal intracerebral hemorrhage. (Stroke. 2009;40[suppl 1]:S16-S19.)

Key Words: amyloid angiography ■ neurovascular unit

By far the most common form of CAA is the Aβ type, defined by the accumulation of aggregated β-amyloid peptide (Aβ) in small cerebral vessels—most prominently the penetrating arterioles of the cortex. Aβ is derived from the amyloid precursor protein (APP) through a series of enzymatic cleavages, and is found in parenchymal plaques of patients with Alzheimer Disease (AD). The 42-aa length Aβ (Aβ42) is principally found in plaques, whereas the shorter Aβ40 is the major form found in CAA. Though CAA is a very common finding in brains of AD patients and is recognized as a histopathologic hallmark of the disease, it is also commonly found in the elderly without AD.¹ One of the most widely recognized complications of CAA is spontaneous intracerebral hemorrhage (ICH), usually involving the cortex or subcortical white matter (“lobar hemorrhage”). This is believed to be a late consequence of disease. More recently, accumulating evidence suggests that CAA may also have effects on vascular reactivity, even at very early stages of the disease. Moreover, there are suggestions that this failure of vascular reactivity may result in chronic ischemia of the white matter within the watershed zone of the most prominently affected penetrating arterioles of the cortex.

Aβ-Induced Cerebral Vessel Dysfunction

The first clues that Aβ may cause substantial vascular impairment stemmed from clinical observations that cerebrovascular abnormalities occur not only in early stages of AD² but also in genetically predisposed patients before the development of AD.³ Subsequent experimental data strongly support this notion. First, soluble Aβ—before its deposition as CAA—was found to be strongly vasoactive (particularly Aβ40). For example, physiologically relevant levels of soluble Aβ40 led to dose-dependent vasoconstriction of isolated cerebral arteries,⁴ and potent vasoactivity was noted when soluble Aβ40 was topically applied to the neocortex of wild-type (WT) mice.⁵ Moreover, young mutant APP mice having elevated levels of soluble Aβ (but no CAA) were shown to have marked cerebrovascular abnormalities, including reduced resting cerebral blood flow (CBF), attenuated CBF response to endothelium-dependent vasodilators, and impaired cerebral autoregulation.⁶ Subsequent studies demonstrated that acute Aβ depletion via γ-secretase inhibition restored cerebrovascular function in young APP mice, further implicating soluble Aβ as the causative factor underlying these in vivo cerebrovascular abnormalities.⁷

Even greater degrees of vascular impairment have been shown when aggregated Aβ deposits within cerebral vessels, as is seen with CAA (Figure 1). Christie and colleagues⁷ were the first to demonstrate this finding—noting severe vasodilatory dysfunction in older APP mice having CAA as compared to young APP mice with no CAA. Others have noted similar age-dependent cerebrovascular deficits in APP mice.⁶,⁸ In addition, we have recently demonstrated a dose response between extent of vascular amyloid deposition and degree of impaired vasomotor function, further implicating CAA in Aβ-induced vessel dysfunction.⁶ Surprisingly, this dose response data also documented that very little CAA (<20% coverage) was required to produce profound vessel dysfunction.⁶ Taken together, these animal data suggest that CAA impairs vascular function to a greater degree than soluble Aβ alone. Accordingly, clinical data have associated CAA with multiple clinical indicators of disease including cognitive impairment on neurological examination,⁹ white matter changes on radiographic studies,¹⁰ and cortical infarcts on pathological analyses,¹¹ whereas no such associations have thus far been identified for soluble Aβ.

Regarding potential underlying mechanism, several key observations have been made. First, CAA-induced vessel...
The function has been identified in the case of soluble Aβ dysfunction.5,12,13 In the case of CAA, molecular studies have only just begun, but early results suggest that ROS and numerous in vitro studies suggest that Aβ-induced vessel dysfunction have recently been investigated. In the case of soluble Aβ, both reactive oxygen species (ROS)5,12 and proinflammatory cascades4 have been implicated. The data supporting ROS is particularly strong, as multiple pharmacological and genetic approaches toward counteracting the effects of ROS—including genetic inactivation of a catalytic subunit of NADPH oxidase—have been shown to reduce or eliminate Aβ-induced cerebrovascular dysfunction.5,12,13 In the case of CAA, molecular studies have only just begun, but early results suggest that ROS and NADPH oxidase may again be significant effectors.8,12

Amyloid Cytotoxicity and Disruption of the ECM

Considerable attention has focused on the neurotoxic properties of Aβ and its aggregates, which has provided support for the amyloid hypothesis of AD. In addition to neurons, numerous in vitro studies suggest that Aβ is toxic to VSMCs,14 human brain pericytes,15 and cerebral endothelial cells (CECs).16 Aβ1–40 was noted to be more toxic than Aβ1–42 in CECs,17 but the opposite was found for SMCs,18 and Aβ with the Dutch mutation (E22Q) was more toxic to SMCs than native Aβ.19 One feature of Aβ which appeared to be related to its toxicity was its ability to aggregate as insoluble amyloid fibrils on the membranes of SMCs. More recent evidence suggests that soluble oligomeric intermediates may also be responsible for cytotoxic activity.

Although in vitro studies indicate that vascular cells are vulnerable to Aβ toxicity, neuropathological and in vivo animal model studies suggest that profound vascular consequences occur even before CAA-related cytotoxicity is observed. Initially, amyloid accumulates at the outer basal lamina in close proximity to SMCs.20,21 At this stage, there are no structural changes to the tunica media and no SMC loss, but progressive and often profound vessel dysfunction can occur (see above). As the disease progresses, amyloid deposits extend into the SMC layer,20,21 leading to significant structural alterations, early SMC loss (Figure 2), and complete vessel shutdown (ie, no functional response to vasodilatory stimuli) (see above). With advanced CAA, the media eventually becomes completely replaced by amyloid and becomes devoid of surviving smooth muscle cells.22 Whereas endothelial cells have abnormal appearance (atrophic cell bodies, irregular nuclei), cell degeneration is not observed until very late in the disease.23 With end-stage disease, amyloid appears to disrupt the basement membrane (BM) and spread to adjacent neuropil forming dyshoric vessels.24

Advanced CAA is often associated with microvascular abnormalities, including microaneurysms with thinning and disruption of the tunica media, as well as fibrinoid necrosis in amyloid-laden vessels.25 Frequently, affected vessels demonstrate a “double barrel” lumen, suggestive of a weakened vascular extracellular matrix (ECM) resulting in the separation of intima from media during tissue preparation.26 Many of these microvascular abnormalities are confined to amyloid-laden segments and observed in the vicinity of hemorrhagic lesions.27 Although these vasculopathies suggest breakdown of vascular ECM and weakening of the vessel wall, the pathogenesis of CAA-related ICH is poorly understood.

Proteases, Amyloid, and Intracerebral Hemorrhage

It has been known for some time that Aβ induces MMP-9 protein and activity in CECs in vitro.28 In addition, recent studies report that mutant Aβ (Dutch mutation) stimulates the expression of uPA and its receptor uPAR,29 and induced MT1-MMP expression in human CECs.30 Both uPA and
MT1-MMP are upstream proteases which are known to activate MMP-9 through a cascade of proteolytic cleavages. We have examined MMP-9 expression in aged APP mice (Tg2576 mice). MMP-9 immunostaining was undetectable in young Tg2576 mice and in aged WT mice. In contrast, increased immunohistochemical staining of MMP-9 was found in amyloid-laden cerebral vessels in aged Tg2576 mice. Furthermore, the vast majority of amyloid-laden vessels that had evidence of prior microhemorrhage demonstrated MMP-9 immunostaining. Given the role of MMP-9 in hemorrhagic transformation following ischemic stroke, these findings raise the possibility that Aβ induces vascular MMP-9 activity which contributes to the development of CAA-related spontaneous hemorrhage.

Though this hypothesis suggests that inhibition of MMP-9 activity as a potential therapeutic target for the prevention of CAA-related hemorrhage, more recent evidence suggests that MMP-9 may play a more complex role than initially thought. In mice, MMP-9 was found to degrade soluble Aβ in the brains of mice; knockout of the gene results in increased levels of brain Aβ. Furthermore, it appears that MMP-9 is capable of degrading aggregated amyloid fibrils and is expressed in activated astrocytes surrounding amyloid plaques in Tg2576 mice. These activities suggest that MMP-9 may play a role in regulating brain Aβ levels and in limiting amyloid plaque growth. Thus, inhibiting its activity may have both salutary as well as detrimental effects.

**Conclusion**

CAA is a neurovascular degenerative disease resulting in progressive dysfunction of the neurovascular unit with increasingly severe clinical consequences (Table). Recent findings support the idea that severe neurovascular dysfunction occurs before significant changes in vascular structure and may lead to chronic white matter ischemia. However, the complication of vascular rupture and spontaneous hemorrhage appears to be a consequence of advanced disease, occurring only after significant cell loss and compromise in structural integrity of the affected arteries. Understanding the relationship between amyloid accumulation and the dysfunction of elements of the neurovascular unit will be important for identifying potential therapeutic targets to prevent these clinical consequences.

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**Disclosures**

None.

**References**


**Table. Progression of CAA**

<table>
<thead>
<tr>
<th>Vascular pathology</th>
<th>Elevated Soluble Aβ</th>
<th>Early CAA</th>
<th>Moderate CAA</th>
<th>Advanced CAA</th>
<th>Dysoric Vessels</th>
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</thead>
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<td>?</td>
<td>Cognitive dysfunction?</td>
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</tbody>
</table>

VSMCs indicates vascular smooth muscle cells; CECs, cerebral endothelial cells.


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