Topical Reviews

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β-Amyloid, Blood Vessels, and Brain Function

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Abstract—Cerebrovascular disease and Alzheimer disease are common diseases of aging and frequently coexist in the same brain. Accumulating evidence suggests that the presence of brain infarction, including silent infarction, influences the course of Alzheimer disease. Conversely, there is evidence that β-amyloid can impair blood vessel function. Vascular β-amyloid deposition, also known as cerebral amyloid angiopathy, is associated with vascular dysfunction in animal and human studies. Alzheimer disease is associated with morphological changes in capillary networks, and soluble β-amyloid produces abnormal vascular responses to physiological and pharmacological stimuli. In this review, we discuss current evidence linking β-amyloid metabolism with vascular function and morphological changes in animals and humans. (Stroke. 2009;40:2601-2606.)

Key Words: Alzheimer disease ■ cerebral amyloid angiopathy ■ vascular cognitive impairment

Medical advances leading to increased life expectancy are causing rapid changes in the medical epidemiology of the elderly. Of major concern is whether gains in years of life will be matched by equal gains in quality of life. Preservation of cognitive function is particularly important. The incidence of dementia and stroke rises exponentially with age. Men at age 65 have a greater than one in 4 chance of developing stroke, dementia, or both; and women at age 65 have a greater than one in 3 chance of developing stroke, dementia, or both.1 The prevalence of cognitive impairment is even greater when including forms of impairment short of dementia.2

Alzheimer disease (AD) and cerebrovascular disease are 2 common pathologies of aging and are the most frequent contributors to cognitive dysfunction. Rather than acting separately, it is now recognized that these pathologies are frequently present in the same brain.3,4 Both demented and nondemented. Autopsy studies suggest that small “silent” infarcts contribute to cognitive impairment,5 and most studies show an additive or synergistic effect in combination with AD pathology.6–8 Clearly there is an urgent need to decipher the relationship between AD and cerebrovascular disease and how they lead to cognitive impairment. Possible links between cerebrovascular pathology and AD pathology have previously been reviewed (for example, by de la Torre).9 We specifically review evidence linking parenchymal and vascular β-amyloid with morphological changes and dysfunction of vessel wall components with a focus on recent animal and human studies.

A link between Aβ and vascular disease is most clearly demonstrated in the case of cerebral amyloid angiopathy (CAA), where deposition of Aβ in the vascular media and adventitia leads to loss of integrity of the vessel wall with resulting brain hemorrhages, both large and small. Well recognized as a cause of brain hemorrhage, CAA is now increasingly recognized as a probable cause of brain ischemia and cognitive impairment independent of stroke.10 Additionally, recent evidence links Aβ with impaired blood vessel morphology and function in the absence of deposition in the vascular media.

Aβ is produced by proteolytic cleavage of the amyloid precursor protein by β-secretase and γ-secretase. Cleavage by these enzymes yields a family of Aβ peptides with a 40-amino acid species (Aβ40) and 42 amino acid species (Aβ42) predominating. Aβ accumulates in the interstitial fluid in correlation with the degree of synaptic activity.11 These peptides may undergo a number of fates (Figure 1).12 They may be degraded by other proteolytic enzymes, including neprilysin and insulin-degrading enzyme. They may remain in solution and enter the plasma through perivascular drainage pathways13 or efflux across the blood–brain barrier.14 Alternatively, they may polymerize to form soluble oligomers or insoluble amyloid fibrils with deposition in the brain parenchyma as senile plaques, as seen in AD, or the vascular media and adventitia, as seen in CAA. In AD, both soluble oligomers and insoluble plaques have been proposed to play a role in neuronal dysfunction.15 We review current evidence...
Cerebral Amyloid Angiopathy

Initially recognized in the context of coexisting AD, it was not until the 1970s that CAA was recognized as a major cause of lobar intracerebral hemorrhage.16,17 The in vivo diagnosis of CAA rests on the demonstration of single or multiple lobar hemorrhages or microbleeds without other evident cause.18 Sporadic and some forms of familial CAA are characterized by deposition of β-amyloid in the media and adventitia of small arteries and capillaries of the leptomeninges and cerebral cortex. White matter vessels are much less affected, and the occipital regions are heavily affected for unclear reasons.19 In contrast to AD, the predominant Aβ species in vascular deposits is the relatively more soluble Aβ40. Although the exact source of vascular amyloid is unknown, it is believed that Aβ is predominantly generated by neurons and then deposited in the vessel wall.20

Numerous pathological studies have demonstrated histological19 and ultrastructural21 abnormalities of the vessel wall in CAA. Loss of smooth muscle cells occurs with replacement of the vascular media by amyloid. There is a direct toxic effect of wild-type and mutant forms of Aβ as demonstrated in cell culture studies.20,22 In addition, recent research using animal models suggests that vascular amyloid decreases adhesion of vascular smooth muscle cells to the basement membrane23 and that capillary amyloid deposition may be associated with capillary occlusion.24

These observations of smooth muscle degeneration and capillary occlusion raise the question of whether cerebral blood flow regulation, dependent on normal vascular endothelial and smooth muscle activity, is impaired in CAA. Indeed, an animal model of CAA shows decreased cortical vascular reactivity to carbon dioxide and whisker stimulation in proportion to the severity of vascular amyloid.25

The concept that CAA alters blood flow is further supported by pathological studies showing an increased prevalence of ischemic lesions in brains with CAA and clinical studies showing that CAA is associated with cognitive impairment independent of the presence of brain hemorrhage, at least partly attributable to ischemia.10 Case–control pathology studies, predominantly performed in brains with a concomitant clinical diagnosis of AD, suggest that severe CAA is associated with small cerebral infarcts independent of age, hypertension, or apolipoprotein E genotype.26–29 The association is particularly strong for microinfarctions, consistent with the involvement by CAA of small arteries and capillaries. In addition, case series show that white matter demyelination, presumably ischemic, may occur.30–32 The severity of CAA has been associated with increased odds of antemortem dementia33 and worse performance on cognitive tests in persons with concomitant AD34 in population-based autopsy studies that simultaneously controlled for severity of AD pathology.

MRI and CT are insensitive to microinfarctions but are arguably more sensitive than autopsy to the presence of white matter lesions. Studies of consecutive patients with CAA presenting with brain hemorrhage show that CT or MRI white matter lesions are common,35 of greater severity than in healthy aging,36 and are associated with cognitive impairment independent of the effects of the brain hemorrhage.35 Familial forms of Aβ CAA also show extensive white matter lesions.37 Newer MRI measurements of water proton diffusion are sensitive to subtle alterations in tissue microarchitecture and show more widespread abnormalities in CAA that represent the combined effects of tissue pathology (eg, white matter lesions and microinfarctions) and its consequences such as demyelination and axonal degeneration.38 In patients with CAA, a whole-brain measure of mean apparent diffusion coefficient may correlate better with cognitive impairment than other MRI markers.39

Altered vascular function has recently been demonstrated in humans with CAA.40 In this pilot study, 11 patients with CAA presenting with stroke or memory symptoms, and diagnosed as having probable CAA using the validated Boston Criteria,18 were compared with 9 healthy control subjects with similar ages and distributions of vascular risk factors. Evoked blood flow velocity in the posterior cerebral artery in response to a visual stimulation task was measured by transcranial Doppler ultrasound and was reduced in the CAA cases compared with control subjects (Figure 2). Among patients with CAA, lower evoked flow velocity response correlated with a higher prevalence of MRI white matter lesions and MRI microbleeds. These data are consistent with observations in a mouse model25 with the exception that in humans, in contrast to the animals, there was little effect of CAA on the evoked response to CO2 measured in the middle cerebral artery. The reason for the differential effects of CAA on visual evoked flow in the posterior cerebral artery, compared with CO2 evoked flow in the middle cerebral artery, could not be determined but could reflect relatively less CAA involvement in the middle cerebral artery territory compared with the posterior cerebral artery territory or the different molecular mechanisms for vasodilation.40

Alzheimer Disease

AD is characterized pathologically by senile plaques, neurofibrillary tangles, and synaptic and neuronal loss. Studies demonstrate that vascular abnormalities also accompany AD,
however, even in the absence of concomitant atherosclerotic vascular disease. The most frequent vascular abnormality seen in AD is CAA. Recent careful studies of capillary morphology and density suggest that a broader spectrum of vascular abnormalities may accompany AD and may be partly independent of CAA. Some have even proposed that vascular dysfunction is a critical early component of Alzheimer pathology. 

Severe Alzheimer pathology is usually accompanied by some degree of CAA. These autopsy studies are supported by MRI studies showing that lobar microbleeds, associated with CAA, are frequently present in the brains of persons with AD although symptomatic lobar intracerebral hemorrhage is rare. The pathology of CAA associated with AD shows differences from the pathology of CAA in the absence of AD, with more frequent capillary relative to arteriolar vascular deposition in the arterial wall. The authors interpreted their data to suggest that capillary CAA is associated with capillary occlusion and decreased blood flow. Other authors have also documented significant arteriolar vascular deposition in addition to capillary deposition, with loss of smooth muscle actin, in AD compared with control subjects. These CAA-related vascular abnormalities may contribute to impaired cognition in AD. In the Honolulu-Asia Aging Study, the combined presence of both moderate–severe CAA and AD on autopsy was associated with greater cognitive impairment in life than the presence of AD alone.

The microvasculature of patients with AD exhibits morphological changes in addition to vascular or perivascular amyloid deposits. Careful autopsy studies show that capillary density, length, and mean diameters are decreased in AD in comparison with similar-aged control subjects, sometimes with segmental narrowing or dilation. An initial quantitative study of hippocampal capillary characteristics between AD and control subjects did not find overall differences, but suggested that associations between AD pathology and capillary morphology may be restricted to the hippocampal subregions most affected by AD. A subsequent study compared hippocampal CA1 and entorhinal cortex capillary parameters with the regional burden of Alzheimer pathology and found that lower total capillary number and lower mean capillary diameter correlated with higher burden of senile plaques and neurofibrillary tangles. Lower mean capillary diameter was independently associated with greater antemortem cognitive disability as measured by the Clinical Dementia Rating scale, even after controlling for the burden of senile plaques and neurofibrillary tangles. Similar observations have recently been published in a transgenic mouse model of AD, in which a vascular corrosion cast was produced by intravascular infusion of a resin followed by removal of the intervening tissue, allowing examination of the 3-dimensional architecture of the microvasculature. Electron microscopy of the cast showed “holes” of decreased capillary density alternating with regions of increased density of morphologically abnormal capillaries.

These observations have led some authors to hypothesize that cerebral hypoperfusion is an early phenomenon in AD that induces neuronal dysfunction and injury. Indeed, cerebral hypoperfusion is observed in both the early and late stages of AD. Although this phenomenon is often attributed to decreased neuronal metabolism or neuronal loss, impaired vascular function may also contribute. Similarly, numerous studies of neuronal activation-associated changes in blood oxygen level dependent response have been interpreted as solely reflecting neuronal function without consideration of possible influences from vascular pathology. There is a relative dearth of physiological studies in AD that examine the vascular response to other stimuli such as carbon dioxide inhalation. A recent study found that middle cerebral artery evoked flow velocity to carbon dioxide, measured by transcranial Doppler ultrasound, was reduced in AD compared with control subjects. By contrast, other blood flow studies have failed to find abnormal vascular reactivity to carbon dioxide in AD, although small sample sizes limit the strength of the conclusions.

**Soluble Aβ and Blood Vessel Function**

Experimental data show that soluble Aβ can cause abnormal vascular reactivity in the absence of vascular deposition or vessel wall dysfunction. These experiments raise the possibility that vascular dysfunction could be an early step in β-amyloid diseases and could even precede significant Aβ deposition. Application of exogenous Aβ to normal blood vessels ex vivo causes endothelium-dependent vasoconstriction. Likewise, application of exogenous Aβ, particularly the Aβ40 species, to the mouse neocortex induces vasoconstriction in vivo. Transgenic mice that overexpress amyloid precursor protein exhibit reductions in cerebral blood flow at an early age, before deposition of Aβ as plaques, and display abnormal vascular autoregulation and attenuation of...
functional hyperemia.63 These effects appear to be mediated by endothelial dysfunction with formation of oxygen free radicals58 by NADPH oxidase.64,65 The finding that soluble Aβ impairs vasodilatory responses in amyloid precursor protein-overexpressing animals has recently been questioned, however,25 and the significance of these experimental findings to human pathophysiology is uncertain at present.

Conclusions and Future Directions

Vascular β-amyloid deposition is a relatively common pathology of aging and is extremely common in person with AD. β-amyloid is directly toxic to smooth muscle cells. Damage to the vessel wall caused by β-amyloid deposits can result in vascular rupture with intracerebral hemorrhage. Aβ-related vascular dysfunction, manifest as impaired vascular responses to stimuli including changes in systemic blood pressure (impaired autoregulation), arterial partial pressure of carbon dioxide, and neuronal activity, seems likely on the basis of experimental evidence but remains underexplored in humans. Vascular dysfunction with reduction in blood flow could be the mechanism by which CAA is associated with microinfarction and small cortical infarcts.

There is a need for further studies to address the relationship among vascular function, brain lesions, and clinical function, including cognition in persons with β-amyloid diseases including CAA and AD. Given the high prevalence of CAA in AD, studies are urgently needed to determine whether CAA is an active player in producing cognitive decline or a bystander. These studies will be aided by careful measurement of β-amyloid disease burden and vascular reactivity.

Thankfully, recent advances in experimental models and human imaging may aid studies of β-amyloid and its effects on the vasculature by allowing more careful serial assessments of β-amyloid burden. The development of mouse models with cranial windows that allow serial amyloid imaging, by multiphoton microscopy,56 will enable longitudinal experimental studies of vascular β-amyloid growth and its determinants. In humans, the development of β-amyloid-binding positron emission tomography ligands offers, for the first time, the ability to measure regional and global β-amyloid deposition in a serial longitudinal manner.67–69 Originally validated as a marker of parenchymal amyloid deposition and AD, it is now clear from autopsy studies that Pittsburgh Compound B55 also binds to vascular β-amyloid.70,71 A small case series suggests that occipital Pittsburgh Compound B retention is relatively greater in CAA compared with AD, consistent with the known topographical distribution in CAA.72 With improved in vivo measurements of β-amyloid, careful physiological investigations of vascular reactivity, and longitudinal study designs, it should be possible to more firmly establish the role of blood vessel function in producing impairment in CAA and AD. The impact of vascular dysfunction on age-related changes in cognition may currently be underestimated. Identification of vascular dysfunction as a significant component of CAA and AD may open up new therapeutic approaches for these currently largely untreatable diseases.

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Disclosures

None.

References


