Amyloid Angiopathy–Related Vascular Cognitive Impairment

Steven M. Greenberg, MD, PhD; M. Edip Gurol, MD; Jonathan Rosand, MD, MS; Eric E. Smith, MD

Abstract—We review accumulating evidence that cerebrovascular amyloid deposition (cerebral amyloid angiopathy [CAA]) is an independent risk factor for cognitive dysfunction. The two population-based autopsy studies that have analyzed cognitive status during life as a function of CAA have each suggested deleterious effects of CAA on cognition even after controlling for age and Alzheimer disease pathology. We also review data from patients with CAA-related intracerebral hemorrhage (the one form of CAA that can be noninvasively recognized) suggesting associations of CAA with radiographic white matter abnormalities and cognitive impairment. These data highlight the importance of elucidating the effects of vascular amyloid on cerebrovascular function and of developing therapeutic strategies for this potentially widespread form of microvascular cognitive impairment. (Stroke. 2004;35[suppl I]:2616-2619.)

Key Words: amyloid ▪ angiopathy ▪ vascular dementia

Cerebral Amyloid Angiopathy and Cognitive Impairment: Population-Based Studies

A notable finding in very severe cases of cerebral amyloid angiopathy (CAA) is cognitive impairment independent of major hemorrhagic stroke. Cognitive impairment has been observed in both familial1–3 and sporadic4,5 instances of severe CAA, generally in the absence of extensive Alzheimer disease (AD) pathology.3,6 These observations suggest that CAA can cause clinically important vascular dysfunction,7 a possibility further supported by multiple studies demonstrating potential mechanisms for β-amyloid–induced vascular damage or functional abnormality.8–12

The presence of cognitive impairment in some forms of severe CAA raises a central question: Does vascular amyloid affect cognition in the large population of elderly patients with lesser extents of CAA? Although generally unrecognized during life, CAA is a very common pathological finding in the elderly. Estimates of the prevalence of CAA from autopsy series are on the order of 10% to 40% in the general elderly population and approximately 80% in brains with accompanying AD.13,14 Whereas autopsy series can be biased by patient selection, a similarly high prevalence of severe CAA in 21% of elderly brains was observed in the population-based Medical Research Council (MRC) clinical-pathologic series, slightly greater than the prevalence of severe neocortical neuritic plaques (19%) in the same series.15

Two population-based studies have addressed the question of the possible effects of CAA on cognition in unselected elderly patients; each study correlated cognitive testing or dementia status of subjects during life with neuropathological findings at autopsy. Among subjects in the MRC study,16 severe CAA was identified in 34 of 93 with dementia versus only 7 of 99 without dementia, yielding an impressively elevated odds ratio (OR) for dementia of 7.7 (95% CI, 3.3 to 20.4). The relationship between CAA and dementia could easily be confounded by potential covariates such as age or the accompanying presence of AD pathology; the magnitude of the odds for dementia (OR, 9.3; 95% CI, 2.7 to 41.0) was no lower, however, in multivariable analysis controlling for age, brain weight, neuritic and diffuse plaques, neocortical and hippocampal neurofibrillary tangles, Lewy bodies, and cerebrovascular disease.

In the population-based Honolulu–Asia Aging Study (HAAS),17 CAA was present in 44% of autopsied brains, which were enriched in pathological findings by the study’s targeting of demented subjects. CAA was nonsignificantly overrepresented in demented (55%) compared with nondemented (38%) brains. When the analysis focused specifically on subjects with AD, the accompanying presence of CAA was found to associate with significantly worse cognitive performance on testing during life. Like the findings in the MRC study, this effect of CAA remained independent in analysis controlling for potential confounders such as age, tangle and plaque counts, infarctions, and apolipoprotein E genotype.

The results of these 2 population-based studies, although not in perfect agreement, support a role of apparently asymptomatic CAA in promoting cognitive dysfunction. The HAAS study points in particular to a possible synergism between AD and the microvascular pathology of CAA, a theme supported by the growing literature regard-
The lack of standardized pathological criteria for rating CAA severity with regard to its effect on cognition make it difficult to compare results across different populations and studies, however, and clearly outlines an obstacle to be addressed by investigators in this field.

Cognitive Impairment Preceding CAA-Related Intracerebral Hemorrhage

An ideal study of CAA and cognition would require a noninvasive method for measuring the presence and severity of CAA in living patients. Despite advances in in vivo imaging of β-amyloid,21 however, this ability has so far remained elusive. The one established method for diagnosing CAA without pathological tissue involves detection of the lobar intracerebral hemorrhages (ICHs) characteristic of advanced CAA,22 typically by sensitive MRI techniques such as gradient-echo imaging.23 The presence of multiple strictly lobar ICHs in an elderly patient without other definite cause of ICH, defined as “probable CAA-related ICH” by the Boston criteria,24 has been shown to correlate with pathologically advanced CAA with high specificity,24 and the number of such hemorrhages to predict risk of both recurrent ICH and overall clinical decline.25

We analyzed cognitive status among 88 consecutive patients (mean age 76.6±8.2) presenting with lobar ICH on admission CT scan and diagnosed with “definite CAA” at autopsy (n=8) or “probable CAA” by gradient-echo MRI (n=64) or brain biopsy/hematoma evacuation (n=16).26 To measure cognitive impairment in this population, we focused on patients’ cognitive status before ICH as determined by family interview in order to avoid the sizable effects of the ICH itself on cognition. We used white matter hypodensity on admission CT as a measure of vascular dysfunction, based on multiple studies demonstrating correlations between radiographic white matter changes, microvascular risk factors, and altered vascular function.27–30

One prominent feature of the CAA cohort was common and severe white matter abnormalities. White matter hypodensity was present in 69 of the 88 patients (78%) and of severe extent (score of 3 or 4 on a 0 to 4 point scale31) in 34 of 88 (39%). White matter score increased with increasing numbers of MRI-detectable hemorrhages (Figure 1A), supporting the possibility that the extent of white matter injury is a function of severity of the underlying CAA-related microvasculopathy.

White matter hypodensity in these patients correlated strongly with the likelihood of pre-ICH cognitive impairment (Figure 1B). Pre-existing cognitive impairment was present in 26 of 88 (30%) patients in the full probable/definite CAA cohort: 9 of 54 (17%) without severe white matter disease versus 17 of 34 (50%) with severe changes (P=0.002). After adjustment for age, severe white matter disease associated with cognitive impairment with an OR of 3.8 (95% CI, 1.4 to 10.6).

Though it is important to note that radiographic white matter disease does not necessarily indicate a vascular cause, the most straightforward explanation for the association between CAA, white matter changes, and cognitive impairment is that advanced CAA causes clinically important vascular dysfunction. These data drawn from a cohort with severe CAA offer a starting point for investigating the more general effects of vascular amyloid on vascular function.

Future Directions

What methods and data do we need to establish the role of CAA in vascular dysfunction and begin to develop treatments? A noninvasive method for identifying nonhemorrhagic CAA would obviously represent a key step toward determining the importance of vascular amyloid in the general elderly population. In this regard, the development of lipophilic molecules that cross the blood–brain barrier and bind to both plaque and cerebrovascular β-amyloid32 is an exciting advance with the potential for imaging CAA as well
as AD pathology. Another approach would be to study patients based on their profile of genetic and environmental risk factors for CAA. This approach is unfortunately limited by our ignorance of most of the factors that predispose to CAA; currently identified risk factors such as apolipoprotein E genotype appear to account for only a small proportion of interpatient variation.

The other major step toward identifying candidate treatments will be to determine the mechanisms that mediate amyloid-dependent vascular dysfunction. Neuropathologically based studies in advanced sporadic or familial CAA have outlined several potential mechanisms, including narrowing of severely affected microvessels, loss of the normal smooth muscle cell layer, and in some cases perivascular inflammation. Other studies based in culture or transgenic mouse systems have identified effects of β-amyloid on cell function that may be more relevant to vascular function in less severe CAA. These mechanisms include changes in gene expression, altered vascular reactivity to physiological stimuli, and appearance of free radicals and markers of oxidative stress. Transgenic mouse models that overexpress the amyloid precursor protein appear to recapitulate all of the major steps characteristic of human CAA, including growth of vascular deposits, abnormal vascular reactivity, and ICH. Parallel studies of vessel function in APP transgenic mice and humans and human brains with CAA may thus prove to be the most promising approach for translating molecular insights regarding β-amyloid into a mechanistic understanding of human CAA.

Acknowledgments

This work is supported by grants from the National Institutes of Health (AG21084, NS42147, NS41409, NS46327, NS42695).

References


Amyloid Angiopathy–Related Vascular Cognitive Impairment
Steven M. Greenberg, M. Edip Gurol, Jonathan Rosand and Eric E. Smith

Stroke. 2004;35:2616-2619; originally published online September 30, 2004;
doi: 10.1161/01.STR.0000143224.36527.44
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/35/11_suppl_1/2616

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/