Converging Pathogenic Mechanisms in Vascular and Neurodegenerative Dementia

Costantino Iadecola, MD; Philip B. Gorelick, MD, MPH, FACP

Dementia is a common neurological syndrome with a major impact on the health and quality of life of the elderly. Although the causes of dementia are numerous, Alzheimer dementia (AD) and vascular dementia (VaD) are responsible for most cases. Recent basic and clinical investigations have provided evidence that AD and VaD, traditionally considered distinct clinical and pathophysiological entities, may share common features. In this brief review, we will present these advances and a synthesis, focusing on the impact that this new information may have on the diagnosis and treatment of these conditions.

Alzheimer Dementia
The neuropathology of AD is characterized by β-amyloid deposition in brain parenchyma and blood vessels and by neurofibrillary tangles. The Aβ peptide derives from a larger protein, the amyloid precursor protein (APP), that is cleaved by the proteases α and β secretases to produce Aβ1-40 and Aβ1-42. In familial forms of AD, mutations in the APP or presenilin genes promote amyloidogenic APP cleavage, leading to increased Aβ production. Present models of AD advocate that Aβ accumulation in the tissue produces the neuronal dysfunction and death that underlies the dementia. However, the mechanisms by which Aβ produces neuronal dysfunction have not been elucidated in full. Although Aβ is well-known to be cytotoxic, recent findings in transgenic mice overexpressing APP have demonstrated that Aβ also has profound effects on cerebrovascular regulation. Resting cerebral blood flow (CBF) is reduced in regions of the cerebral cortex and in the hippocampus of APP mice. The cerebral vessels of these mice do not respond to vasodilating agents, such as acetylcholine, that act by releasing endothelium-dependent relaxing factors. APP mice are unable to keep CBF constant during moderate hypotension or hypertension, indicating a disturbance in cerebrovascular autoregulation. Furthermore, the increase in CBF produced by neural activation, a fundamental homeostatic mechanism that matches brain activity with substrate delivery, is profoundly attenuated in APP mice. Such cerebrovascular dysfunction occurs in the absence of amyloid deposition in brain or blood vessels and is fully developed before mice exhibit signs of cognitive impairment. Pharmacological treatment with free radical scavengers or overexpression of superoxide dismutase in APP mice abolishes the cerebrovascular impairment, indicating that it is mediated by overproduction of free radicals. Therefore, APP overexpression and Aβ produce cerebrovascular alterations that are related to oxidative stress. Furthermore, evidence has been provided that inflammatory mediators promote some of these cerebrovascular alterations. These data in transgenic mice are in agreement with recent finding of reduced response to activation in presymptomatic patients at risk for AD, indicating that the cerebrovascular alterations are an early event in the course of the disease. Thus, Aβ in addition to its toxic neuronal effects produces vascular dysregulation.

These findings in mice and humans support the long-held view that vascular insufficiency contributes to the pathobiology of AD. The reduced vascular response to activation may limit the supply of substrates and oxygen to active neurons, resulting in alterations in the cerebral microenvironment and neuronal dysfunction. Alterations in cerebrovascular autoregulation have important implications for the functional and structural integrity of the brain. Loss of autoregulation renders the brain more susceptible to reductions in arterial pressure, such as those occurring in sleep. Thus, reductions in arterial pressure that would not alter cerebral perfusion in the normal brain may lead to cerebral ischemia in the presence of Aβ. Hypoperfusion-related ischemia would be most marked in the periventricular white matter, a region supplied by arterioles with limited collateral flow. Thus, an impairment in autoregulation could contribute to the periventricular white matter lesions that are frequently observed in patients with AD.

Overlap Between Vascular Factors and Neurodegeneration in the Mechanisms of Dementia
Early diagnostic criteria for VaD emphasized cerebrovascular arteriosclerosis as a root cause of dementia. However, Tomlinson et al found that volumes of >50 mL of infarcted tissue might be associated with dementia and invariably >100 mL of infarcted tissue was associated with dementia. Based in part on the findings of xenon cerebral blood flow studies in degenerative and vascular cases, Hachinski et al coined the term multi-infarct dementia. These studies helped to fuel a shift in thinking away from the concept of hardening of the arteries in favor of multiple infarcts.
also noted that degenerative, vascular, or a combination of these neuropathologic changes could occur in normal individuals and dementia might occur when the neuropathologic changes were less substantial. Thus, multifactorial causation was a possibility, and lower volumes of infarction might be associated with dementia. More recently, data from several clinical studies emphasized that the presence of ischemic lesions enhanced the cognitive deficits in patients with AD pathology. Thus, cerebral ischemia worsens the effects of AD pathology on cognitive function. Experimental data support this possibility. Cerebral ischemia upregulates the expression of APP in otherwise healthy rats. Furthermore, there is evidence that ischemia enhances the cleavage of the Aβ peptide from APP. Therefore, the ischemic process enhances Aβ cleavage, thereby amplifying cytotoxicity. Aβ could also promote the release of inflammatory mediators that exacerbate postischemic inflammation and contribute to cerebrovascular dysfunction. Although it is unknown whether ischemia-induced Aβ production leads to amyloid plaque formation, the data in APP mice without plaques suggest that nondeposited Aβ is sufficient to produce vascular and cognitive impairment. This is in accord with the suggestion that Aβ oligomers, rather than amyloid plaques, are responsible for the neuronal dysfunction and cognitive impairment.

Another development has been the realization that AD and VaD share common risk factors. Case-control studies, cohort studies, and clinical trials have suggested that vascular risk factors might be important in both AD and VaD. For example, midlife arterial pressure elevation has been associated with later-life morphological brain changes and cognitive decline. In addition, control of arterial pressure may result in reduction of both AD and VaD. Other vascular risk factors, such as diabetes mellitus, hyperhomocystinemia, and cigarette smoking, may also be important in the pathogenesis of VaD and AD.

Conclusions

We have reviewed experimental and clinical evidence suggesting that AD and VaD have many common features. Experimental data suggest that in AD, as in VaD, there is perturbation of cerebral blood flow and its regulation. Such vascular dysregulation is mediated by Aβ, a major causative factor of AD. The deleterious cerebrovascular effects of Aβ raise the possibility that vascular factors play an adjuvant role in the mechanisms of AD by amplifying or promoting the neurotoxic effects of this peptide (Figure). Clinical studies suggest that AD and VaD share common cerebrovascular risk factors, such as, for example, hypertension, diabetes, hypercholesterolemia, and hyperhomocystinemia. This finding suggests that the deleterious vascular effects of these risk factors play a role both in AD and VaD. Consequently, risk factor modification can be a valuable preventive strategy in AD, as in VaD.

On the other hand, experimental studies suggest that ischemia upregulates APP and increases the production of Aβ. Therefore, in VaD, as in AD, Aβ may promote neuronal dysfunction through its direct neurotoxic effect (Figure). Both in AD and VaD, cerebrovascular dysfunction disrupts the delicate balance between the brain’s energy requirements and the blood supply and renders the brain more vulnerable to injury. The evidence that ischemic stroke promotes dementia in cases with minimal AD pathology supports the view that the pathogenic factors at the basis of both diseases are synergistic rather than simply additive. In addition to their pathogenic significance, measures of CBF may be used for the early diagnosis of dementia. However, the evidence suggests that reductions in CBF and alterations in vascular regulation can occur in both conditions. Therefore, the traditional view that alterations in CBF can be used to distinguish VaD from AD needs to be reevaluated. Finally, inflammation and vascular oxidative stress occur both in AD and VaD and are likely to play a role in the disease process. This observation provides a rationale for reevaluating the role of antiinflammatory agents and antioxidants as a therapeutic strategy for these conditions.

Acknowledgments

C. Iadecola supported by research grants from the NIH and is the recipient of a Javits Awards from NIH/NINDS. Dr Gorelick is supported by NIH subcontract No. RO1 NS33430 (NINDS) and RO1 AG17934 (NIA) and the MR Bauer Foundation.

References


24. Iadecola and Gorelick Converging Pathogenic Mechanisms in VD and VaD 337


Key Words: Alzheimer disease ■ cognitive disorders ■ stroke ■ vascular reactivity
Converging Pathogenic Mechanisms in Vascular and Neurodegenerative Dementia
Costantino Iadecola and Philip B. Gorelick

Stroke. 2003;34:335-337
doi: 10.1161/01.STR.0000054050.51530.76
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 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/34/2/335

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/