Vascular Cognitive Impairment

Vascular Cognitive Impairment: Small Vessels, Big Toll

Introduction

Sandra Black, MD, FRCP(C); Costantino Iadecola, MD

This year’s Princeton conference featured a session on vascular cognitive impairment (VCI), signaling recognition, a long time in coming, of this important consequence of cerebrovascular disease. The emphasis was on cerebrovascular dysregulation and small vessel white matter disease, drawing from animal models, human pathology, neuroimaging, epidemiology, and the recent clinical trial in CADASIL, as summarized below.

Cerebrovascular oxidative stress from reactive oxygen species mediated by NADPH oxidase present in cerebral vessels may be the final common pathway of the cerebrovascular dysregulation induced by aging, Alzheimer disease (AD), and hypertension, according to Iadecola and colleagues.1 Cerebral energy demands are serviced through control mechanisms such as functional hyperemia and cerebrovascular autoregulation, which tailor the blood supply to tissue needs and maintain perfusion over a wide range of blood pressures. Aging changes the structure and vasodilatory capacity of vessels, increasing susceptibility to ischemia. Chronic hypertension induces remodeling and stenosis of the arteries and fibrinoid necrosis of the arterioles, alters cerebrovascular reactivity, and shifts autoregulation to the right, increasing vulnerability to hypotension, as well as attenuating functional hyperemia. Amyloid beta (Aβ), the peptide produced in toxic amounts in AD, is also vasculopathic, disrupting vascular endothelium and myocytes, obliterating capillaries and, likewise, impairing functional hyperemia and autoregulation. Fibrillar Aβ deposits around arterioles, weakens the muscular wall, and conduces both to hemorrhage and occlusion. These vasculopathic effects of aging, hypertension, and Aβ, acting alone or in concert, lead to hypoperfusion, blood brain barrier dysfunction, compromised protein synthesis and synaptic plasticity, and eventually neuronal death with cognitive consequences along the way. Oxidative stress is therefore an important potential target for intervention.

As discussed by Black et al.,2 the cognitive phenotype of this chronic small vessel disease includes slowed information processing, impaired executive function, and gait difficulty. Neuroimaging reveals this to be a visible but relatively silent cerebrovascular disorder. Lesion burden can be quantified, preferably by techniques that generate tissue volumes for all the cerebral brain compartments, and probed by newer imaging techniques that measure microstructural integrity, metabolism, and can even tag fibrillar Aβ. Coregistered postmortem MR and pathology, aided by immunohistochemical methods, have elucidated substrates of white matter disease at the cellular level. Even small lacunes connote active small vessel disease, as harbingers of future clinical stroke and cognitive decline. In nonnecrotic lesions of white matter, the neurovascular unit is besieged not only by hypoperfusion, related to arteriopathy (driven by aging, hypertension, Aβ, genetics,1 diabetes4 and other vascular assailants), but also by breaches of the blood brain barrier and vasogenic edema. This is primed by periventricular venous collagensesis and ependymal leakage, which increase with aging, and by amyloid congestion of the perivascular highways in those predisposed to AD. Brain bog leads to mind fog, and the ubiquity of these white matter changes in aging humans threatens independent longevity of ourgraying population.

Diabetes interacts with aging, hypertension, Aβ, and apolipoprotein E e4 as another guerrilla fighter in the small vessel insurgency targeting brain health and cognition. Mechanisms are many, involving oxidative stress, inflammation, angioneurins, and large vessel and microvascular disease.4 In two large population studies, the Honolulu Asia Aging Study and the Age Gene/Environment Susceptibility-Reykjavik Study, associations between diabetes and both vascular and Alzheimer brain changes have been described, and brain outcomes are finally being added in clinical treatment trials of diabetes.4

As succinctly summarized by Dichgans,3 CADASIL is a genetically-determined “pure” form of subcortical ischemic vascular dementia of young onset, iconic in the field of VCI, because it is often unaccompanied by the vascular risk factors typical of sporadic disease. Its cognitive profile and neuroimaging correlates have been well described, including the importance of atrophy as well as lesion quantification, Magnetization Transfer ratio, and Diffusion Tensor Imaging measures. While a recent multinational clinical trial of donepezil, led by Dichgans, found no significant effects on

Received and accepted September 16, 2008.

From the Heart and Stroke Foundation Centre for Stroke Recovery and Departments of Medicine (Neurology) (S.B.), Sunnybrook Health Sciences Centre, University of Toronto, Canada; and the Division of Neurobiology, Department of Neurology and Neuroscience (C.I.), Weill Medical College of Cornell University, NY.

Correspondence to Sandra E. Black, MD, FRCP(C), Brill Professor of Neurology, Department of Medicine, Cognitive Neurology, A421, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N 3M5. E-mail sandra.black@sunnybrook.ca

(Stroke. 2009;40[suppl 1]:S38–S39.)

© 2009 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.108.537712
the primary end points, treated patients performed better on some executive tasks and timed measures, though the clinical significance of these findings were unclear.

In summary, progress in molecular neurobiology, neuroimaging, population studies, clinical-imaging-pathological series, and clinical trials is advancing understanding of the neurovascular substrates of VCI. New targets are emerging, and, given the boomer demographics, the need for aggressive management of traditional vascular risk factors as well as for new treatments has never been greater.

**Sources of Funding**
Supported by the Canadian Institutes of Health Research (MT13129), Heart and Stroke Foundation Centre for Stroke Recovery, Alzheimer Association US, Alzheimer Society of Canada, the L.C. Campbell Cognitive Neurology Research Unit and Brill Chair in Neurology, Dept of Medicine and Sunnybrook Health Science Centre, U of Toronto, Toronto, Canada (to S.E.B.); National Institutes of Health (NS37853, HL18974) and a Javits Award from NIH/NINDS (to C.I.).

**Disclosures**
None.

**References**

**Key Words:** vascular cognitive impairment ■ oxidative stress ■ hypertension ■ aging ■ Alzheimer disease ■ venous collagenosis ■ diabetes ■ CADASIL.
Vascular Cognitive Impairment: Small Vessels, Big Toll: Introduction
Sandra Black and Costantino Iadecola

Stroke. 2009;40:S38-S39; originally published online December 8, 2008;
doi: 10.1161/STRK.108.537712
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/40/3_suppl_1/S38

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/