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 induced by aging, Alzheimer disease (AD), and hypertension, according to Iadecola and colleagues. Cerebrovascular disease. The emphasis was on cerebrovascular dysregulation induced by aging, Alzheimer disease (AD), and hypertension, according to Iadecola and colleagues. Cerebrovascular dysregulation induced by aging, Alzheimer disease (AD), and hypertension, according to Iadecola and colleagues.

Cerebrovascular oxidative stress from reactive oxygen species mediated by NADPH oxidase present in cerebral vessels may be the final common pathway of the 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, diabetes and other vascular assailants), but also by breaches of the blood brain barrier and vasogenic edema. This is primed by periventricular venous collagenson 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 our graying population.

Cerebrovascular oxidative stress from reactive oxygen species mediated by NADPH oxidase present in cerebral vessels may be the final common pathway of the 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, diabetes and other vascular assailants), but also by breaches of the blood brain barrier and vasogenic edema. This is primed by periventricular venous collagenson 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 our graying population.

Diabetes interacts with aging, hypertension, Aβ, and apolipoprotein E e4 as another guerilla 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. 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.

As succinctly summarized by Dichgans, 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...
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/STRKEAHA.108.537712

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