Vascular Cognitive Impairment: Small Vessels, Big Toll

Introduction

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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 collagenosis andependymal 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 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
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.

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References

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