Vascular Contributions to Cognitive Impairment in Late Life

Helena C. Chui, MD[a,*], Liliana Ramirez Gomez, MD[b]

KEYWORDS

• Vascular cognitive impairment • Vascular dementia • Diagnosis • Treatment
• Neuropathology • MRI • White matter hyperintensity • Silent brain infarct

KEY POINTS

- A multifactorial approach to cognitive impairment in late life (eg, vascular, neurodegenerative, and systemic factors) may be more appropriate than the traditional dichotomous classifications (eg, vascular cognitive impairment vs Alzheimer disease).
- Quantitative neuroimaging enables detection of silent brain infarcts and white matter changes before onset of clinical symptoms.
- Multimodal imaging (eg, structural MRI combined with diffusion tensor tractography) can show the anatomically distributed effects of discrete infarcts.
- Amyloid PET imaging helps to identify concomitant Alzheimer conditions in persons with vascular brain injury.
- Management of vascular risk factors remains a proven and practical approach to reducing acute and progressive cognitive impairment and dementia.

BACKGROUND

History

The perceived contribution of vascular factors to cognitive impairment has oscillated significantly during the last century. In the early 20th century, progressive loss of intellectual function in late life was ascribed to hardening of the arteries, or so-called arteriosclerotic dementia. Alzheimer disease (AD) was considered a rare early-onset dementia associated with neurofibrillary tangles and senile plaques. When Tomlinson and colleagues[1] observed profuse tangle and plaques in sporadic, late-onset,

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[a] Department of Neurology, University of Southern California, 1540 Alcazar Street, CHP215, Los Angeles, CA 90033, USA; [b] Department of Neurology, University of California San Francisco, 400 Parnassus Avenue, A871, San Francisco, CA 94143, USA
* Corresponding author.
E-mail address: Helena.Chui@med.usc.edu

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dementia cases, AD, not arteriosclerosis, became the preeminent etiology. Abrupt-onset, stepwise decline in cognition caused by acute strokes constituted the conceptual basis for multi-infarct dementia. Slowly progressive dementia caused by severe arteriopathy and demyelination of subcortical white matter, or Binswanger syndrome, was considered rare. In the 1980s, the landscape shifted with the advent of structural imaging. Asymptomatic white matter hyperintensities (WMH) and silent brain infarcts (SBI) were discovered on brain MRI in 20% to 30% of nondemented, community-dwelling, elderly subjects.[2] The ability to detect early and subclinical vascular disease without overt dementia prompted an earlier designation, vascular cognitive impairment (VCI). In the 1990s, epidemiologic studies noted associations between stroke risk factors and cognitive impairment (absent history of symptomatic stroke) and led to the still-unproven notion that vascular factors might promote Alzheimer disease. More recently, the frequent co-occurrence of vascular and AD conditions (15% between ages 65 and 89; 30% after age 90 years), suggests that a multifactorial, rather than dichotomous, approach to diagnosis and treatment may better reflect the realities of progressive cognitive impairment in late life.

Concepts

VCI is a syndrome or phenotype, not a disease. At its simplest, VCI embodies the concept that cognitive impairment is caused by vascular brain injury (VBI). The pathways leading from risk factors to cerebrovascular disease (CVD) to VBI are widely heterogeneous. Common sporadic forms of CVD include atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy (CAA); rare genetic forms of CVD include CADASIL (cerebral autosomal dominant arteriopathy subcortical infarcts and leukoencephalopathy), and CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy).[3] VBI may result from ischemia and hemorrhage and toxic, inflammatory, and oxidative stress.[4] To prevent or mitigate VCI, efforts must be directed toward risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and smoking.

G&E → VRF → CVD → VBI → VCI

Genetic & Environmental factors → vascular risk factors → cerebrovascular disease → vascular brain injury → vascular cognitive impairment

The likelihood that VBI contributes to cognitive impairment varies with the patient and nature of the vascular insult. Location within cognitive networks and number and size of lesions are important determinants of the type and severity of cognitive impairment. For executive function, networks of parallel, frontal-subcortical circuits were first described based on anatomic studies in nonhuman primates.[5] Recently, Jeon and colleagues[6] scrutinized these parallel prefrontal-caudate-thalamic circuits in humans using task-activated high field 7T functional MRI combined with diffusion tensor imaging (**Fig. 1**). For the higher level branching executive tasks, activations were found in the ventroanterior portion of the prefrontal cortex (PFC), the head of the caudate nucleus, and the ventral anterior nucleus in the thalamus. Conversely, for the lower-level episodic executive tasks, activations were located in the posterior region of the PFC, the body of the caudate nucleus, and the medial dorsal nucleus in the thalamus. When lacunar infarcts and WMH occur in these frontal-subcortical circuits, impairment in executive function is likely to follow.

Co-occurrence of vascular and neurodegenerative pathologies (such as AD [amyloidopathy and tauopathy] and Lewy body disease [α-synucleinopathy]) occurs frequently, especially with increasing age. Macro- and microinfarcts are each found in approximately 30% of elderly persons, often combined with AD conditions.[7–9] Converging evidence indicates that ischemic infarcts and neurodegenerative lesions