CEREBROVASCULAR CONTRIBUTIONS TO COGNITIVE IMPAIRMENT & DEMENTIA

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Summary: Stroke and cerebrovascular (CVD) imaging lesions are common in the elderly and increase with advancing age. However, only a minority of elderly have stroke or visible CVD imaging lesions. In those individuals, CVD is often a contributor, but rarely a sole cause, of cognitive impairment. CVD acts in an additive manner with other pathologies, particularly those of Alzheimer disease (AD). The clinical diagnosis of a vascular contribution to cognitive impairment and its presumed relevance can be inferred from: (a) history of stroke especially when the onset of cognitive impairment is temporally related to the stroke; (b) a history of cardiovascular disease (coronary artery disease, congestive heart failure, atrial fibrillation, myocardial infarct); (c) presence of vascular risk factors (especially diabetes, hypertension, cigarette smoking); and (d) imaging evidence of white matter hyperintensities (WMH) or infarcts. However, all of these features are indirect measures of the true impact of CVD on cognition: the CVD lesion that is most proximate to cognitive decline is not certain. Microinfarcts, disconnection via WM disruption or cortical thinning are candidate mechanisms. The physics of MR make it unlikely that we will be able to image microinfarcts in life, but improved imaging techniques such as diffusion tensor imaging may add to our ability to diagnosis white matter dysfunction. Reduction of the vascular contribution to cognition is feasible now, through management or avoidance in midlife of vascular risk factors.

Understanding the cerebrovascular contribution to later life cognitive has undergone a transformation in the past decade. Rather than conceptualizing an entity of "vascular dementia" as present or absent, the emerging concept of the vascular contribution to cognitive impairment (VCCI) envisions a collaborative, supportive and additive role for cerebrovascular disease in late life cognitive impairment in conjunction with other diseases, especially Alzheimer's disease (AD).

Some vascular pathology exists in 29% to 41% of dementia cases coming to autopsy in population-based cohorts, but though only 9% to 10% have only vascular pathology to account for their dementia[1-4]. Cerebrovascular disease usually occurs in the setting of concomitant neurodegenerative diseases especially Alzheimer's disease[4-7]. Antemortem studies are now able to recognize biomarkers for both AD and cerebrovascular disease. For example, a study of cognitively impaired patients with multiple infarcts on MR imaging showed that about a third also had abnormal amyloid imaging using amyloid PET[8]. When AD and CVD occur together their effect is additive not multiplicative on cognition[9].

The conceptual change has an empiric basis. The NINDS-AIREN diagnostic criteria[10] based on the "big, known stroke" model have had poor predictive value[1,3,11-13]. Specifically, while a history of a stroke is undoubtedly a risk factor for future cognitive decline[14-19], a history of overt stroke is uncommon in persons with a high burden of cerebrovascular disease[20]. Second, the notion that there is a distinct cognitive profile of "vascular dementia" is a naive over-simplification. While it is the case that cognitive slowing and abulia are characteristic of vascular dementia and memory impairment is less evident[21], those features are neither specific nor sensitive[22]. The notion of "abrupt onset" as a diagnostic feature of cerebrovascular etiology of cognitive impairment is of limited value, as are so-called "focal neurological signs." Both are too nonspecific. While a history of cognitive impairment that closely follows an overt stroke is a reliable marker of relevant CVD, persons with that profile constitute on a

small fraction of VCCI. Most VCCI has no distinctive temporal profile: it can exhibit plateaus as well as steady decline.

Imaging evidence of cerebrovascular disease captures much more covert pathology than is evident from clinical history alone. Good quality MR imaging is essential for diagnosing cerebrovascular pathology. However, imaging evidence of white matter hyperintensities, small (lacunar) or larger infarcts or cortical microbleeds are better thought of on a continuum of risk rather than as categorical indicators of certain relevance for cognitive impairment. Both lacunar infarcts[23-26] and white matter hyperintensities[27-31] are more common in persons with cognitive impairment than in cognitively normal elderly, but a large fraction of the latter may have such lesions.

Table 1 summarizes the major clinical and imaging features that support a diagnosis of a vascular contribution to cognitive impairment. Table 1 represents the author's own scheme, not one that has any been adopted by any consensus group.

The critical lesion causing cognitive impairment in cerebrovascular disease remains elusive, and in fact, might be more than one entity. Large vessel extracranial disease of the carotid or vertebrobasilar systems are not the proximal cause of cognitive impairment. White matter hyperintensities are neither specific nor sensitive enough to represent the critical lesion for cerebrovascular cognitive impairment. Nor is a single lacunar infarct. Instead, both white matter hyperintensities and lacunar infarcts might be best thought of as proxies for some underlying critical pathology. Extensive white matter ischemic disease could lead to cortical disconnection and thus induce cognitive impairment,[32,33] but diffusion tensor imaging rather than T2 weighted scans may better detect the critical pathology. Microinfarcts are a strong candidate for being a core lesion of VCI.[34] Imaging evidence of cerebrovascular disease can be used to infer microvascular pathology, but MR imaging at present cannot diagnose microinfarcts because most microinfarcts are smaller than the resolution of 3T MRI, ie <1 mm in diameter

Table 1. **An Index of Cerebrovascular Disease in Cognitive Impairment** (from [35])

Not supportive - Low Probability of CVD	Supportive- Moderate Probability of CVD	Most strongly supportive- High Probability of CVD
No history of stroke	Any stroke above midbrain by history, without subsequent impact on cognition	Stroke temporally related to onset of dementia or worsening of cognition
One focal sign (eg an unexplained extensor toe sign or a reflex asymmetry)	2 or 3 neurologic signs suggestive of cerebrovascular origin	Multiple neurologic signs strongly suggestive of cerebrovascular origin
White matter Hyperintensities -None or minimal	White matter Hyperintensities - Mild to moderate	White matter Hyperintensities -Severe
None or one lacune	2 to 3 Lacunes	4 or more Lacunes
No cortical infarcts or only one small cortical infarct	Cortical infarct, single	Cortical infarcts, large, multiple
No infarcts in critical regions	Lacune or small infarct only in critical regions	Hippocampal, caudate, thalamic infarct larger than lacune

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