Brain Vascular Disease Overt and Covert

W.T. Longstreth, Jr, MD, MPH

Editorial

See related article, pages 2116–2120

Work from the Leukoaraiosis and Disability (LADIS) Study Group1 and from others characterizing brain structure and function in the elderly continue to challenge myopic views of how vascular disease affects the brain. What most often demands attention and consumes resources—patients with symptoms and signs of stroke and transient ischemic attack—represents the easily recognized tip of the iceberg whose larger underwater mass goes largely ignored. More needs to be learned about covert vascular disease that erodes brain structure and function in ways less dramatic than overt disease.

Before sophisticated imaging revealed details of brain structure, symptoms and signs defined brain vascular disease. Postmortem examinations of the brain were limited to a select group of patients but foreshadowed the existence of substantial subclinical vascular disease.2 With the introduction of brain imaging, clinicians could characterize the structure of the brain in patients with acute symptoms and signs. Those with symptomatic brain vascular disease were often found on brain imaging to have other vascular lesions that had not caused acute symptoms. Brain imaging in some patients with reversible clinical syndromes such as transient ischemic attacks showed findings compatible with an acute infarct. Perhaps not surprisingly, such patients may have a prognosis different from those whose imaging is clean.3

As brain imaging, especially with magnetic resonance imaging (MRI), of those with or without symptoms and signs of brain vascular disease became more ubiquitous, the realization grew that subclinical infarcts and white matter hyperintensities were prevalent among the elderly and likely related to ischemic vascular disease. Systematic brain imaging has now been done in populations of elderly people without symptomatic brain vascular disease such as in the Framingham Study,4 the Rotterdam Study,5 the Cardiovascular Health Study,6 and others, or in elderly people with minor symptoms and minor disability such as the LADIS Study.1 The conclusions are consistent. The MRI findings of infarcts and white matter hyperintensities are common, and even more so in select groups such as in the LADIS Study. Furthermore, the findings cannot be considered as benign accompaniments of aging in that they are associated with dysfunction of the brain, especially cognition. These covert MRI findings associated with subtle brain dysfunction are more common than overt disease.7,8

The strength of associations between brain structure and function has likely been underestimated because of crude measures used in many studies, including the LADIS Study. The relations may become clearer as more precise measures of the MRI findings and of brain functions, not limited to cognition, become the routine in such research. For example, investigators in The Netherlands have used an automated system, the Brain-O-Matic, to calculate precise volumes of infarcts and white matter hyperintensities.9 Other investigators have shown that quantitative assessment of gait is associated with MRI findings.10 The imaging findings of frailty are starting to be defined.

If you accept that these MRI findings are common in the elderly and not benign, can they be prevented with preservation of brain function? The next step is to identify etiologic risk factors. Some may be genetic11 and not be directly modifiable, but may still provide clues as to how to reduce erosion of brain structure and function. Blood pressure likely plays a critical role as a modifiable, etiologic risk factor.12 We may need to know more about a person’s blood pressure than a measurement or 2 in the clinic. For example, even after controlling for the baseline blood pressure, investigators have shown that the response of the blood pressure to emotional stress is related to MRI findings13 and to cognitive function.14 Similarly, the pattern of blood pressure measured over 24 hours—with nocturnal dipping, nondipping, or reverse dipping—is associated with MRI findings.15 A role for homocysteine continues to be explored.16 In most studies, diabetes mellitus and lipids seem to be playing minor roles. Statins do not seem to help. In a recent report from the PROSPER Study Group, worsening of white matter hyperintensities was documented over 33 months but was similar in those treated with a statin or not.9

One way to advance the field more rapidly would be to include a quantitative brain imaging substudy in any clinical trial evaluating any treatment of vascular disease in any organ. The substudy would be appropriately powered for the more common occurrence of the brain MRI findings compared with other outcomes. The surrogate outcome of MRI findings would need to be supplemented with precise measures of brain function, especially cognition and gait. Such efforts have already begun10,12 but should be expanded by those whose highest priority is preservation of the brain’s structure and function.

References


KEY WORDS: extremities ■ vascular disease