Really small vascular disease of the brain

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The diagnosis of cerebrovascular disease has changed dramatically over the past several decades with the introduction of CT and MRI. These technologies have made it apparent that "silent" cerebral infarction (i.e., without an associated history of TIA or stroke) is more prevalent than clinically symptomatic infarction. Between 8% and 20% of people 50–75 years of age have such findings.[1] In the Cardiovascular Health Study (CHS), an ongoing epidemiologic study of cardiovascular risk factors in the elderly, 28% of seniors, average age 75 years, had "silent" infarcts on MRI scanning,[2] and ~18% of those without baseline silent strokes on MRI had new "silent" infarcts on a 5-year follow-up MRI.[3] Several studies have shown that these "silent" infarcts are not benign. In the Rotterdam study, a longitudinal study of 1,000 healthy elderly between ages 60 and 90 years who were followed for 4 years, participants with baseline "silent" infarcts (≥3 mm) had more rapid cognitive decline than those without infarcts, with twice the risk of incident dementia.[4] In the CHS study, approximately 87% of silent infarcts on follow-up MRI were 3–20 mm, of which 20% were ≤5 mm. This subgroup demonstrated higher levels of upper and lower extremity dysfunction than those without such lesions, as well as greater declines in tests of cognitive function.[2,3]

Theories pertaining to the etiology of small brain infarcts have varied but 2 possible causes have been emphasized: those caused by microatheroma of larger small vessels and those caused by lipohyalinosis of the smallest of the brain's blood vessels. The latter are characterized by vessel wall thickening from fibrinoid necrosis with resultant reduction in luminal diameter. Given the difficulties of studying the brain microvasculature, these hypotheses have remained largely unproven. In this issue of *Neurology*®, Bezerra and colleagues[5] present new data that indirectly support these theories. Using data from the Atherosclerosis Risk in Communities Study (ARIC), the authors studied which risk factors were associated with infarct–like lesions (ILLs) of differing lesion size. They studied lesions ≤20 mm in maximum dimension located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, deep cerebellar white matter, centrum semiovale, or corona radiate. ILLs that were ≤7 mm in diameter (including those ≤3 mm) were hypothesized to be due to lipohyalinosis. Those that were 8–20 mm were hypothesized to reflect microatheromatous disease. If their hypothesis was correct, one would expect differences in the risk factors associated with each size of lesion. This was indeed the case. The authors found that very small lesions, including those ≤3 mm, were associated with diabetes or elevated HbA1c level. Metabolic factors are known to affect the very small blood vessel function (endothelial dysfunction) and lumen size. The larger lesions were more strongly associated with low-density lipoprotein cholesterol. The latter is a risk factor linked to large vessel atherosclerosis. Both types of lesions shared the common risk factors of increasing age, hypertension, and smoking.

Aside from providing a better understanding of the pathophysiology of small brain infarcts, the distinction between small and very small brain infarcts is important for several other reasons. First, the distinction between the 2 forms of small vessel disease may explain why most studies of lacunar infarcts have found diabetes to be an important risk factor for small infarcts, but not all studies agree.[4,5] Second, in the last few years it has become appreciated that microvascular disease is a systemic illness, much the way atherosclerosis is a systemic disease of the large, medium, and large small arteries. Microvascular disease of the eye and the kidney are associated with microvascular disease of the brain. In ARIC retinal arteriolar narrowing and arteriovenous nicking were associated with impaired executive function and psychomotor speed.[6] In the ACCORD and TRANSCEND studies, albuminuria was cross-sectionally and prospectively associated with incident

See page 102

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cognitive decline.[7] Third, appreciation of the systemic nature of microvascular illness helps explain why people with diabetes, who have an inordinately high prevalence of small vessel disease, are prone to cognitive impairment, independent of large vessel disease. It is estimated that people with diabetes are almost twice as likely to have impaired cognition as people without diabetes.[8] Finally, the knowledge that disease of the very small blood vessels, as compared to atherosclerotic vascular disease, is injurious to brain health creates the awareness and hope that interventions that ameliorate microvascular complications in one microvascular bed may be beneficial to the brain microcirculation. Recently, a small study of a new antioxidant showed that the compound halted, and even reversed, diabetic kidney disease, a disorder of the glomerular small blood vessels.[9] Were a larger study of diabetic kidney disease to prove effective, it is possible that this therapy, or a related medication, may have benefit for brain function in the context of microvascular illness. The cerebral and renal circulations are characterized by high flow and low impedance. Autoregulation of the microvasculature serves to bring blood flow to these organs, at the same time limiting excess pressure exposure in the capillaries.[10] Endothelial dysfunction and loss of microvascular autoregulation can disrupt the normal milieu within the extracellular matrix of the brain and kidney.

Bezerra and colleagues are to be congratulated for bringing to the reader's attention the distinction between sort-of-small and really small vascular disease of the brain. It is hoped that this new knowledge will lead to more targeted research that will ultimately translate into less neurologic disease in the future.

AUTHOR CONTRIBUTIONS

Dr. Nyquist: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Dr. Barzilay: drafting/revising the manuscript.

DISCLOSURE

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