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Invited Commentary

Invited Commentary: Albuminuria and Microvascular Disease of the Brain—A Shared Pathophysiology

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This commentary considers the implications of the association between albuminuria and cognitive decline described by Jassal et al. in this issue of the *Journal* (*Am J Epidemiol*. 2010;171(3):290–291). The authors report that men with albuminuria had a greater likelihood than men without albuminuria of experiencing declines in cognitive function over a 6.6-year period. Albuminuria is the result of endothelial damage in the kidney, which, in turn, is the result of microvascular disease. If one of the key mechanisms of brain microvascular disease is leakage of serum proteins into the brain extracellular space, in a fashion parallel to albuminuria that occurs in nephrosclerosis, several facets of cerebrovascular disease and cognitive decline are explained. First, brain microvascular disease would not be recognized by traditional clinical features of cerebrovascular disease because brain microvascular disease occurs gradually and insidiously. Second, the extravasation of serum proteins as a result of brain microvascular disease would account for the perivascular distribution of white matter hyperintensities on magnetic resonance imaging. Albuminuria might be a useful screening test for generalized microvascular disease and, if detected, might reasonably prompt brain imaging and more intensive therapeutic efforts to forestall further endothelial dysfunction in the kidney, brain, and elsewhere.

aged; albuminuria; cognition; dementia; dementia, vascular

In this issue of the *Journal*, Jassal et al. (1) report that, in a cohort of 1,345 elders, those men with albuminuria were more likely than men without albuminuria to experience declines in cognitive function over a 6.6-year interval. The association was not found for women. Their study has a number of strengths, including its longitudinal design, large sample size, and multi-instrument cognitive assessment battery. The lack of association between albuminuria and cognitive decline in women was puzzling, and not fully explained. Nonetheless, the associations between albuminuria and cognitive decline in men were very consistent across multiple analytic approaches. The findings of Jassal et al. add to a growing body of work (2–6) that supports an association in older persons between changes in kidney function and changes in brain function. Why is it that something in the urine has anything to do with brain function? The answer lies in how and why protein gets into the urine.

More so than glomerular filtration rate, the relation between microalbuminuria and vascular diseases of the kidney holds unique insights relevant to cerebrovascular disease. Both the brain and the kidney are highly vascular structures that respond to diseases such as hypertension and diabetes mellitus in similar ways at the microscopic level. In nephrosclerosis, gradual alterations in the kidney endothelial cells, glomeruli, and interstitial spaces lead to glomerular leakage of serum proteins into the urine (7, 8). If a similar process were occurring at the endothelial level in brain microvessels, serum proteins would pass into the brain extracellular space. Neuropathologic studies show that white matter hyperintensities represent enlarged perivascular spaces and perivascular demyelination (9). These changes are what one might expect if the brain extracellular spaces were exposed to proinflammatory proteins that, in health, should remain inside the vascular space. While there is no direct proof that this process occurs, my colleagues and I (10) and others (11, 12) have previously shown that white matter hyperintensities are indeed associated with microalbuminuria.

The association of albuminuria and cognition has much broader implications for understanding the role of

cerebrovascular disease in late-life cognitive impairment. Cerebrovascular disease has long been recognized as playing some role in dementia. The consensus view has swung from the era of ''hardening of the arteries'' to a period when there was frank disdain for the notion that cerebrovascular disease played any important role at all. Now, the consensus view is that cerebrovascular disease plays some role in late-life dementia, but just how much is very difficult to define (13). Brain microvascular disease is relatively common neuropathologically (14–17). However, in epidemiologic studies (18), the number of cases of dementia that can be labeled as substantially stroke related is rather small. One reason for the low detection rate in clinical studies is the well-recognized lack of sensitivity of clinical markers of stroke-related dementia (19–22). A history of stroke causing cognitive impairment and the presence of infarcts on imaging are simply insensitive for identifying those patients with genuine cerebrovascular pathology.

One hypothesis for why markers of overt cerebrovascular disease are insensitive is that *macro*vascular disease is only part of the picture. Microvascular disease of the brain is not being captured in clinical diagnostic assessments because it does not cause overt strokes and infarcts visible on neuroimaging. Brain microvascular disease, like microvascular disease of the kidney, is associated with conditions such as diabetes and hypertension. However, assigning a cerebrovascular etiology to a patient with progressive cognitive impairment on the basis of the presence of vascular risk factors is far too nonspecific. Very mild or benign forms of glucose intolerance or hypertension may have no material impact on brain or kidney microvascular structure and function. Markers of brain microvascular disease that are both specific and sensitive are badly needed.

This is where microalbuminuria as a result of nephrosclerosis fits in: because the kidney is exposed to the same vascular pathophysiologic processes as the brain in diseases such as diabetes, hypertension, or hypercholesterolemia conditions, the kidney is telling us what is happening in the brain. Brain microvascular disease alters brain structure by virtue of the consequences of endothelial disease and extravasation of blood proteins into the brain extracellular spaces. This process occurs gradually but steadily and eventually leads to cognitive decline. There is nothing stroke-like in the insidious appearance of microvascular disease in the brain. Moreover, the changes on neuroimaging are not those of large infarcts. White matter hyperintensities and lacunar infarction—visible lesions that are more closely related to brain microvascular disease than large-vessel distribution infarcts—appear in a clinically silent fashion, just as nephrosclerosis does.

The endothelial dysfunction–serum protein extravasation hypothesis addresses at least one way that microvascular disease could cause brain injury. However, the evidence does not address the quantitative impact of brain microvascular disease on cognition. The rate of cognitive change observed in nondemented persons in the study of Jassal et al. (1) may not proceed linearly. The amount of cognitive impairment attributable to microvascular disease could accelerate if the protein extravasation process itself induced further vascular injury. On the other hand, the microvascular-related cognitive impairment could decelerate if glucose intolerance or high blood pressure ameliorated with aging. Future studies of the role of brain microvascular disease in late-life dementia are going to have to use a direct measure of microvascular disease that captures the pathology more precisely than current neuroimaging. Diffusion tensor imaging may be one strategy to better assess the impact of microvascular disease on brain white matter (23). Diffusion tensor imaging detects changes in normal-appearing white matter and might therefore be more sensitive and specific than white matter hyperintensities for pathology (23). Noninvasive measurements of cerebral blood flow in response to physiologic challenges (24) might be another strategy. At the same time, amyloid imaging to gauge the burden of Alzheimer pathology would be necessary as well to promote understanding of the unique impact of microvascular disease on cognition.

The basis for the link between albuminuria and brain dysfunction needs much more investigation. Vascular risk factors themselves are associated with cognitive decline (25–28). There is evidence directly linking diabetes to Alzheimer pathology (29), and there are similar data on hypertension (30). It is possible that the associations between cognition and albuminuria observed by Jassal et al. (1) were simply a result of shared variance with other vascular risk factors and not specific to the pathophysiology of microalbuminuria. The authors' own analyses did not support such an interpretation, however. Parsimony makes it at least plausible that diabetes and hypertension act on the same vascular mechanisms in all vascular beds. Endothelial dysfunction is a plausible common denominator for both brain and kidney.

Albuminuria can be measured easily and inexpensively. In contrast, whereas brain magnetic resonance imaging is noninvasive, it is hardly inexpensive. Therefore, with the increasing evidence for an association between albuminuria and brain health, a clinically relevant outcome of the current study is that albuminuria could prove to be a useful initial *screening* test for the presence of generalized endothelial dysfunction and could prompt further investigations of the brain. Mechanistically, the processes leading to microalbuminuria tell us something very worthwhile about potential parallel processes in the brain. Early detection of brain endothelial dysfunction could lead to meaningful interventions far before overt cognitive deterioration occurred.

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