Lessons About Brain Vascular Disease From Another Pulsating Organ, the Kidney

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See related article, pages 55–61.

Because of similarities in the vascular supply to kidney and brain, information about vascular disease in one organ may inform us about vascular disease in the other, and such knowledge may shed light on ways to treat or prevent these diseases. Unlike most organs, both kidney and brain are low resistance end-organs and are exposed to high-volume blood flow throughout the cardiac cycle, explaining their pulsating nature. For the kidney, impairments from vascular disease manifest as problems with glomerular filtration, detected clinically by biochemical markers such as serum creatinine, urinary albumin, and serum cystatin C. For the brain, impairments manifest with overt focal neurologic deficits, such as with stroke or transient ischemic attack, or as covert global deficits affecting cognition, mobility and mood, such as has been suggested with small-vessel disease. In humans, investigation of brain vascular disease and how it causes impairment of brain function often entails looking at the structure of the brain with MRI for infarctions, white matter lesions, and volumes of brain, ventricles and sulci. Given the difficulty in getting tissue, exploration of cause usually does not include microscopic examination of brain tissue, although microinfarcts inapparent on MRI can be identified. For investigation of vascular disease in the kidney, structural changes detectable on imaging are limited primarily to decrements in kidney size due to chronic fibrosis and atrophy. On the other hand, tissue is more readily available than from the brain and shows vascular changes analogous to those described in the brain, including arteriolar intima-media thickening and hyalinosis.

In support of the idea that one organ may tell us about the other, Ikram and colleagues describe cross-sectional associations of renal function and MRI-defined findings of brain vascular disease in a population-based cohort of 484 older adults with a mean age of 73 years from the Rotterdam Scan Study. Mean estimated glomerular filtration rate (eGFR) based on serum creatinine and other variables was 58 mL/min per 1.73 m² indicating that a substantial proportion had impaired renal function, defined by eGFR being <60 mL/min per 1.73 m². Lower renal function was correlated with a smaller volume of normal white matter, especially deep rather than lobar, and a larger volume of white matter lesions, estimated using an automated volumetric technique. In contrast, eGFR was not associated with MRI-defined infarct after adjustment for vascular risk factors.

Others have also described associations between vascular disease of the kidney and brain. At one extreme, patients with end-stage renal disease, defined by an eGFR <15 mL/min per 1.73 m² or kidney replacement therapy, are at 3 to 9 times greater risk for stroke compared with the general population, even after accounting for age, gender and race. Among patients with end-stage renal disease without a history of stroke or transient ischemic attacks, about 50% have MRI-defined infarcts, and those harboring covert brain infarcts are at significantly increased risk of future overt vascular events compared with those whose MRI are free of infarcts. An excess of white matter lesions have also been found on the MRI of patients with end-stage renal disease. In individuals with mild to moderate chronic kidney disease not requiring dialysis, 30% to 60% excess risk of clinically overt stroke has also been reported, even after adjustment for common stroke risk factors. This association has been demonstrated in hypertensive patients, as well as in population-based cohorts. Risks of covert MRI-defined infarcts and white matter lesions are also increased. In the Cardiovascular Health Study of community-dwelling adults age 65 years and older, prevalence of MRI-defined infarcts was higher in those with impaired kidney function compared with those without, as measured by cystatin C but not as measured by creatinine. Such observations raise questions about whether cystatin C may be superior to creatinine as a measure of impaired kidney function that relates to risk of future vascular events. As would be predicted by these studies, associations between measures of kidney function and brain function, namely dementia and cognitive decline, have also been described.

Possibly some shared risk factor such as diabetes or hypertension could lead to a similar vascular injury in both kidney and brain and explain these associations. Diabetes seems unlikely to have an important role given how few of the participants in the population-based studies have this condition, specifically <5% in the Rotterdam Scan study described here. Hypertension is the obvious choice but in most studies adjustment in statistical models for hypertension does not eliminate the association. Nevertheless, differences in duration and long-term control of hypertension are usually not considered in large cohort studies of vascular disease. Even if one accounted for long-term control of peripheral blood pressure, differences in some other aspect of blood pressure may exist, such as central aortic pressure or diurnal variations in blood pressure. Impaired renal function is associated with

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the loss of the normal nocturnal drop in blood pressure, so called “dipping”, and diurnal variations in blood pressure have been associated with MRI-defined small-vessel disease.\(^{19,20}\) Also unknown are genetic factors that may make kidney and brain more susceptible or resistant to common vascular risk factors.

Rather than simply shared insults, perhaps impairments of kidney function lead to brain injury directly or indirectly by modifying the effects of some risk factor. For example, with impaired kidney function, levels of endogenous inhibitors of nitric oxide synthase are increased, and metabolites of nitric oxide are decreased.\(^{21}\) Nitric oxide regulates microcirculation and blood-brain barrier,\(^{9,22}\) both of which have been implicated in the development of white matter lesions and other manifestations of brain small-vessel disease.\(^{23}\) Endothelial dysfunction of the conduit arteries—in part as a result of this reduced nitric oxide availability—is also common in kidney disease\(^{24}\) and might plausibly contribute to small-vessel disease of the brain.\(^{25}\) A similar argument could be made for homocysteine and inflammation, which increase with impaired kidney function and have been associated with MRI-defined small-vessel disease. Nonetheless, the associations in the current Rotterdam Scan Study persisted after adjustment for levels of homocysteine and C-reactive protein,\(^{5}\) suggesting other as yet unidentified factors have more important mediating effects.

The accumulating evidence, to which the work of Ikram and colleagues\(^{5}\) can now be added, indicates a link between vascular disease of the kidney and brain. Challenges remain in deciding what are the most appropriate measures of impaired function in these organs. Whether kidney and brain share unique susceptibilities to vascular injury, especially from central aortic pressure,\(^{1}\) or whether impaired kidney function itself contributes to impaired brain function requires clarification of molecular and genetic mechanisms. Understanding the interplay of vascular disease in these 2 organs holds the promise of finding novel means to reduce the risk of impaired function, especially in the brain. The path to this understanding begins with the type of study reported by Ikram and colleagues and requires continued collaboration of nephrologists and neurologists.

### Disclosures

Both authors are co-investigators in the Cardiovascular Health Study.

### References


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