Kidney Medicine

Albuminuria, Cognitive Impairment, and Structural Brain Disease: Connecting the Brain and Kidney

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Cognitive impairment is increasingly recognized as a common and progressive complication of chronic kidney disease (CKD).[1] Cognitive impairment appears to occur at least twice as often in individuals with CKD as in the general population, with a reported prevalence of 10%-40%, depending on the stage of CKD as well as the cognitive test used for diagnosis.[2-4] Multiple prior studies have shown that low estimated glomerular filtration rate (eGFR) is a strong, independent risk factor for the development of cognitive impairment.[2,5] Indeed, the severity and prevalence of cognitive impairment increase as kidney function declines, with dialysis patients at highest risk.[2,6] Due to a rising prevalence of CKD and an aging population, it is all but certain that the number of patients with concomitant CKD and cognitive impairment will increase over time.

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Decreased eGFR is only half of the current definition for staging CKD. The presence and severity of albuminuria is as powerful a risk factor for all of the key clinical outcomes in kidney disease patients, including kidney failure, mortality, and cardiovascular disease. Albuminuria is also a risk factor for cognitive impairment. Several prior studies have examined the association of urine albumin with both cognitive function and structural brain findings. Weiner et al[7] reported that in a cohort of 335 homebound elders, albuminuria was associated with poorer executive function (but not memory) and a greater burden of white matter hyperintensities, a marker of early cerebrovascular disease. Similarly, Tamura et al[8] examined the association of albuminuria with incident cognitive impairment within the Reasons for Geographic and Racial Disparities in Stroke Study, a large cohort of over 19,000 community dwelling adults. They found a strong association between albuminuria and incident cognitive impairment, largely in individuals with higher eGFR values. Both studies adjusted analyses for demographics, education, and cardiovascular disease risk factors.

In this month's issue of *Kidney Medicine*, Maki et al[9] build on this prior literature regarding albuminuria, cognitive impairment, and structural brain disease. The Japan Prospective Studies Collaboration for Aging and Dementia is a large community-based cohort of nearly 12,000 participants. All participants had eGFR and urine albuminuria assessed at baseline. As part of prespecified study goals, participants were also assessed by study investigators for mild cognitive impairment using a widely accepted clinical definition and a central adjudication committee. Impressively, over 10,000 of the enrolled participants underwent magnetic resonance imaging scans. The scans were automatically assessed using a software package, which allowed for calculation of total brain volume, white and gray matter volume, and the volumes of specific brain regions of interest such as the hippocampus.

The researchers found that higher albuminuria levels were significantly associated with structural brain disease, including lower total brain volume and greater volume of white matter hyperintensities. Adjusting for potential confounders, including demographics, education, diabetes, and prior stroke, led to some attenuation, but a trend across albuminuria strata remained significant. In contrast, eGFR demonstrated a much weaker association with brain volume and white matter disease. A nearly identical pattern was observed with eGFR, albuminuria, and mild cognitive impairment. Albuminuria was a strong risk factor for mild cognitive impairment, regardless of adjustment for potential confounding factors. Low eGFR, in contrast, was not a risk for mild cognitive impairment, even in unadjusted analyses.

What can explain these findings? Albuminuria is well accepted as an early indicator of microvascular disease.[10] Other organs besides the kidney that share similar vascular physiology also appear to be negatively impacted by the clinical conditions that lead to CKD. For example, it is well known that that diabetic retinopathy and nephropathy have a shared pathophysiology.[11] The same appears to be true for the blood vessels in the brain.[12] White matter disease is an early manifestation of cerebrovascular disease,[13,14] and therefore it is not surprising that albuminuria is strongly associated with white matter hyperintensities. Patients with CKD typically have been exposed to traditional vascular disease risk factors that increase in prevalence as kidney function declines as well as nontraditional risk factors such as mineral and bone disease[15,16], inflammation[17], and uremic toxins.[18,19]

In contrast to albuminuria, the lack of association seen with eGFR is likely explained by a lack of statistical power; only 66 individuals in the cohort had an eGFR of less than 30 mL/min/1.73 m^2, making it difficult to draw a conclusion at the lower levels of eGFR. Prior studies, including the Reasons for Geographic and Racial Disparities in Stroke Study discussed above, the Chronic Renal Insufficiency Cohort,[20] and the Rotterdam study,[21] recruited significantly more individuals with lower eGFR levels, allowing detection of an association with cognitive impairment. Despite this limitation, the authors are to be commended for their work. Their study represents one of the largest cohorts assembled with both assessment of

kidney function (eGFR) and kidney damage (albuminuria) as well as structural brain disease (imaging) and functional brain disease (cognitive testing). Their findings cement the idea that albuminuria is a strong risk factor for both structural and clinical neurologic findings, particularly before kidney disease reaches its most advanced stages. Assessment of urine albumin remains our most powerful tool for early detection and treatment of CKD and its complications.

ARTICLE INFORMATION

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