Kidney Disease and Brain Health: Current Knowledge and Next Steps

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The growing public health burden of nondialysis chronic kidney disease (CKD) as the population ages is mirrored by concomitant cerebrovascular and neurodegenerative aging changes on brain magnetic resonance imaging (MRI) and associated cognitive impairment in CKD. Cerebrovascular changes in CKD are demonstrated by microvascular white matter changes; decreased white matter integrity, reflecting microvascular disease in the kidney; and micro- and macroinfarcts. Neurodegenerative changes are represented by decreased cortical gray matter volume, or atrophy of the cerebral lobes (especially temporal and frontal in Alzheimer disease [AD] and related dementias), and enlarged ventricular volume. Multiple investigations of the relation between kidney function in nondialysis CKD, assessed using estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR), and cognitive impairment have demonstrated a consistent graded association between decreasing kidney function and cognitive decline.[1] This relationship is especially strong below an eGFR of 45 mL/min/1.73 m^2; also, moderate-to-severe cognitive impairment is more prevalent below an eGFR of 30 mL/min/1.73 m^2 and, independently, with an elevated UACR (>30 mg/g).[1–3] Recent brain imaging studies in patients with CKD have identified similar associations between these kidney biomarkers and the structural brain changes underlying cognitive impairment in CKD.[4–6] Overall, while cerebrovascular and neurodegenerative brain changes on MRI are both observed in patients with CKD, a larger cerebrovascular component has been reported.[6] Thus, CKD is often considered a model of accelerated vascular brain aging.[7]

Related Article, p. ***

In this issue of *AJKD*, Scheppach et al[8] have made an important contribution toward further elucidation of the underlying brain changes that occur in patients with CKD in reporting the results of a large brain MRI study. The authors conducted a cross-sectional examination of the relationship between kidney function and brain MRI abnormalities in a subcohort of 1,527 participants from the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) with MRI scans. The mean age of the study cohort was 76 years, 58% were women, and 27% were African American. Less than half of the cohort was classified as having CKD, as the cohort's median eGFR was 60.8 (IQR, 47.6-73.7) mL/min/1.73 m^2 and median UACR was 10.5 (IQR, 6.4-22.6) mg/g. About 34% of the cohort had mild cognitive impairment and only 5.0% had dementia at baseline. Exposure measures were eGFR and log(UACR). Cortical volume reduction, infarcts, micro-hemorrhages, and white matter hyperintensities and white matter integrity (using diffusor tensor imaging measures) were used as brain MRI outcomes in multivariable linear and logistic regression models. They also evaluated whether the associations varied when different biomarkers (cystatin C, creatinine, combination of creatinine and cystatin C or β_2-microglobulin) were used to estimate GFR.

The main finding of this study was that lower eGFR and higher UACR are associated with lower brain volume, or atrophy. However, the degree of atrophy seen in regions susceptible to neurodegenerative pathologies, including AD and limbic-predominant age-related TDP-43 encephalopathy (LATE, a disease characterized by onset at ages 80+, similar memory and word finding symptoms as in AD, and TDP-43 protein accumulations in amygdala and similar regions to AD), were similar to the degree of atrophy seen in the rest of the cortex. These findings suggest that some of the brain atrophy observed is not likely primarily due to neurodegenerative etiologies like AD and LATE but due to a combination of etiologies including cerebrovascular disease. This is not surprising, as the findings of any MRI study reflect the composition of the study population. In this case, slightly less than half of participants had CKD (most with mild CKD), corresponding to a relatively lower expected contribution of cerebrovascular disease pathologies. The relatively low (5%) prevalence of dementia for a cohort with a mean age of 76 years (compared to expected approximately 10% in non-CKD populations) also suggests a lower expected contribution of both advanced cerebrovascular disease neurodegeneration.[9] Additionally, the authors confirmed previous reports that both lower eGFR and higher UACR were associated with greater burden of microvascular disease, reflected by greater white matter hyperintensities and impaired white matter microstructural integrity on diffusion MRI. Though UACR and eGFR are highly correlated, only higher levels of UACR (a measure of vascular endothelial inflammation) had increased odds of cortical and lacunar brain infarcts and brain micro-hemorrhages, also confirming some prior studies. Importantly, the authors also found no interaction between race and the observed associations, and found that effect sizes were generally similar in direction and magnitude in comparing the eGFRs calculated with each of the 4 biomarkers described above.

Even after accounting for common cardiovascular risk factors, Scheppach et al found that there was global brain atrophy—not specific to regions typically affected by AD or LATE—and that kidney disease was associated with greater amounts of macro- and microcerebrovascular disease (greater white matter disease, brain infarcts, and

microhemorrhages).[8] The findings regarding cortical atrophy build on our nascent understanding gained from previous studies of the complex mechanisms underlying the widespread cortical thinning (another measure of atrophy) seen in CKD, independent of vascular dysfunction. For example, in one study, the lowest quartile of eGFR (31-60 mL/min/1.73 m^2), compared to the highest (>83 mL/min/1.73 m^2), was associated with cortical thinning in patients with AD, independent of cerebrovascular pathologies.[10] In another study, the risk of cortical thinning was higher in those with cognitive impairment and lower in those who did not carry the APOE4 allele (a gene strongly associated with increased risk of AD).[11]

The observation that the associations between kidney measures and structural brain MRI changes did not vary by race is an especially important contribution of this study, as brain MRI studies inclusive of substantial proportions of African American participants are lacking, despite the higher incidence of CKD[12] and dementia in African American populations.[13] Furthermore, the systematic comparison of different biomarkers used for eGFR calculation increases generalizability of the results and confirms that the observed associations are not substantially affected by how eGFR is calculated. In addition, the greater information provided by UACR in comparison to eGFR in associations with cerebrovascular brain changes reflects that higher UACR may be better at capturing endothelial damage and, thus, microvascular damage, confirming a prior study.[5] Other strengths of this study are the large, well-characterized population including classification of cognitive impairment severity, as well as robust 3.0 T MRI methodology and statistical modeling.

There is widespread consensus that kidney disease and brain health are highly interlinked, and that these associations underlie the increased prevalence of cognitive impairment seen in CKD, driven primarily—but not solely—by cerebrovascular pathologies. However, 3 avenues of "next steps" research would help disentangle the multiple interrelated pathways that lead to cognitive impairment and associated cortical atrophy and cerebrovascular brain changes in CKD. First, large longitudinal MRI studies are needed to track the progression of these brain changes and shed light on the causal relationships between kidney and brain function. These studies must include diverse older populations, in which at least 50% have moderate-to-severe CKD and 10%-15% moderate-to-severe cognitive impairment, to enable better characterization of structural brain changes association with cognitive impairment in CKD populations. Second, longitudinal positron emission tomography (PET) imaging for amyloid and tau deposition in patients with CKD and cognitive impairment could be harnessed to more accurately capture the trajectory of regional changes due to AD and other neurodegenerative pathologies as CKD progresses; to our knowledge, only amyloid PET has been used thus far.[14] Third, imaging studies that incorporate traditional and novel mechanistic biomarkers as exposures could advance our understanding of the pathways underlying the cortical thinning seen in CKD. These include biomarkers of both kidney metabolic mechanisms (inflammation and oxidative stress, anemia, altered bone-vascular axis) and of kidney tubular injury,[15] and the newer blood-based biomarkers of AD and related pathologies. In that arena, CKD was associated with higher levels of the blood-based biomarker p-tau181 and 217 in a large cohort study of patients with AD and other neurodegenerative pathologies (as defined on PET scans), compared to those without CKD.[16] Although these elevated levels may be due to their decreased clearance, similar studies with sequential biomarker levels could help clarify this association. Overall, large longitudinal studies incorporating improved methods are required to allow us to account for the complex contributions of kidney disease to the risk of dementia more precisely.

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