The Official Journal of the National Kidney Foundation
AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES
VOL 52, NO 2, AUGUST 2008

EDITORIALS

The Cognition–Kidney Disease Connection: Lessons From Population-Based Studies in the United States

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As the proportion of elderly individuals in the US population rises, chronic diseases that affect the elderly are assuming increasing importance; these conditions include both chronic kidney disease (CKD) and cognitive impairment.[1,2] In this issue of the *American Journal of Kidney Diseases*, researchers explore the relationship between these 2 conditions in large, population-based, elderly US cohorts.[3,4] Both studies reveal an independent and graded association between CKD and cognitive functioning; but what is the basis and the significance of the cognition–kidney disease connection?

WHAT ARE COGNITIVE IMPAIRMENT AND DEMENTIA?

Cognitive impairment describes a spectrum of disease ranging from minimal cognitive deficits that may occur with relatively normal aging to mild cognitive impairment to severe dementia; the most common causes of cognitive impairment and dementia are Alzheimer disease pathology, cerebrovascular disease, or a combination of these. The estimated prevalence of mild cognitive impairment, defined as cognitive decline greater than expected for an individual's age and education level that does not interfere notably with activities of daily life, ranges from 3% to 20% in individuals aged 65 years and older.[5] Dementia is characterized by acquired impairment in multiple behavioral and neuropsychological domains including memory, language and speech, visuospatial ability, cognition, and mood or personality, with the requirement that this impairment interfere with daily activities; dementia prevalence in the United States is as high as 6% to 10% among individuals aged 65 years and older.[6] While over half of dementia cases are classified as Alzheimer disease, where memory is more prominently affected, the majority of non-Alzheimer dementia is related to vascular causes. Differentiating between Alzheimer disease and vascular dementia is often difficult, as there is likely significant overlap between these entities, with vascular lesions modifying Alzheimer disease expression and vice versa.[7]

Cognitive impairment may be due to vascular disease alone, and, in the setting of repeated vascular insults, may progress to vascular dementia. Accordingly, cognitive impairment due to vascular disease may exhibit a step-wise onset, frequently develops in the absence of clinically recognized stroke, occurs in the setting of small-vessel cerebrovascular disease often without focal neurologic deficits, and typically manifests with executive function deficits (eg, managing and adjusting a medication regimen).[8] Brain imaging in individuals with cognitive impairment can reveal large volume infarcts, lacunes, leukoaraiosis (synonymous with white matter disease), and any combination of the above, all of which could suggest a cerebrovascular etiology.[5,9,10]

Address correspondence to Daniel E. Weiner, MD, MS, Division of Nephrology, Tufts Medical Center Box #391, 800 Washington St, Boston, MA 02111. E-mail: dweiner@tuftsmedicalcenter.org

0272-6386/08/5202-0001$34.00/0
doi:10.1053/j.ajkd.2008.05.003

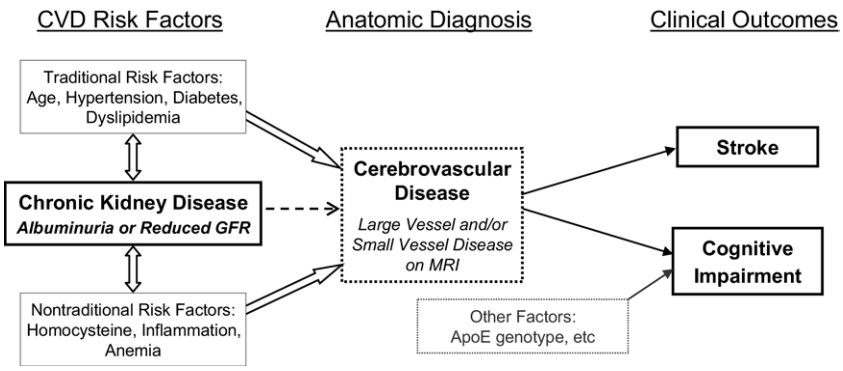

Figure 1. Conceptual diagram of the development of cerebrovascular disease in CKD, presenting the transition from cardiovascular disease risk factors, including CKD, to clinical outcomes of cerebrovascular disease, including stroke and cognitive impairment.

THE COGNITION–KIDNEY DISEASE CONNECTION

CKD is a risk state for cardiovascular disease and cerebrovascular disease in large part because of the high prevalence of traditional cardiovascular disease risk factors in patients with reduced kidney function, including older age, diabetes, hypertension, and dyslipidemia.[11,12] Like CKD, cognitive impairment is also associated with cardiovascular disease risk factors. Hypertension, diabetes, and dyslipidemia are all associated with cognitive decline,[13-16] most notably in the setting of small-vessel cerebrovascular disease.[17] The relationship between nonvascular dementia, specifically Alzheimer disease, and both cerebrovascular disease and vascular disease risk factors is less clear, with some studies showing no association between cognition and hypertension[18-20] while others have found associations between cognitive impairment and traditional cardiovascular disease risk factors including hypertension and hyperlipidemia.[21,22] Other risk factors may contribute—several studies have shown associations between nontraditional cardiovascular disease risk factors, including hyperhomocysteinemia and inflammation, with subsequent cognitive decline. Notably, these findings are less consistent than seen for traditional risk factors and studies did not typically account for kidney disease.[23,24] Given the known associations of CKD with cardiovascular and cerebrovascular disease, it follows that CKD, defined by reduced glomerular filtration rate (GFR) and/or albuminuria, could be associated with further manifestations of cerebrovascular disease beyond overt stroke, namely cognitive impairment. As presented in Fig 1, this association may be mediated through factors intrinsic to or exacerbated by CKD, or may represent parallel manifestations of systemic vascular disease concurrently affecting 2 different vascular organs—the brain and the kidney—with albuminuria and reduced GFR both readily ascertained markers of systemic vascular disease.

STUDIES EVALUATING THE COGNITION–KIDNEY DISEASE CONNECTION

In this issue of *AJKD*, 2 large population-based studies further explore this connection. Barzilay et al examined the cross-sectional association between urine albumin-creatinine ratio and cognitive impairment in individuals from the Cardiovascular Health Study (CHS) who participated in the Cardiovascular Health Cognition Study.[3] They first screened individuals using the Modified Mini-Mental State Examination (3MS) between 1991 and 1994 and later selectively administered a more extensive cognitive battery in 1998 and 1999 to all African American participants and the higher-risk white participants; 2,389 (74%) participants undergoing extensive cognitive testing had provided urine samples approximately 2 years prior to this testing, although 73 of these individuals were excluded as dementia diagnosis predated initial cognitive screening. The results of this study are impressive: with each doubling of urine albumin-creatinine ratio, the risk of mild cognitive impairment increased by 10% and dementia increased by 22% in univariate analysis. The association of albuminuria with dementia remained significant in multivariable analysis. This result is likely driven by vascular changes, as the authors further demonstrate that the presence of albumin-creatinine ratio greater than 30 mg/g is associated with higher white-matter hyperintensity grade and the strength of the association between albuminuria and dementia is higher for the vascular dementia

subtype. There are weaknesses to this study, most notably the lack of concurrent assessment of cognitive function, albuminuria, and brain imaging. While this introduces potential ascertainment biases, these factors most likely bias toward not finding a relationship as dementia, albuminuria, and cerebrovascular disease are all risk factors for death.

Kurella-Tamura et al examined the cross-sectional association between estimated GFR and cognitive impairment in individuals from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study.[4] They assessed cognitive impairment in 23,405 people aged 65 and older using a relatively crude but easily administered tool—the 6-item screener—which includes 3 questions assessing orientation and 3 questions assessing memory; cognitive impairment was defined by 4 or fewer correct answers. Despite the limitations of this cognitive tool, the investigators found a sharp and graded rise in the prevalence of cognitive impairment at lower estimated GFR levels. In adjusted analyses, each 10-mL/min/1.73 m^2 decrease in estimated GFR below 60 mL/min/1.73 m^2 was associated with an 11% increase in prevalence of impairment (OR, 1.11; 95% confidence interval, 1.04 to 1.19). There are several weaknesses to this study, most notably the limitations of the cognitive assessment procedure which utilized a screening instrument rather than detailed neuropsychologic testing, limiting the ability to better define the severity and nature of cognitive impairment in the REGARDS participants.

Prior to the studies by Barzilay et al and Kurella Tamura et al in this issue of *AJKD*, there were limited evaluations of cognition in individuals with kidney disease. In a prior study evaluating the CHS cohort, Seliger et al reported that kidney disease, defined by baseline serum creatinine greater than 1.3 mg/dL in women and greater than 1.5 mg/dL in men, was associated with an increased risk of developing vascular dementia but not Alzheimer dementia in elders who reported baseline good or excellent health.[25] This was an important finding as it offered information both on the prevalence of cognitive impairment and allowed hypothesis generation as to the mechanism of cognitive impairment in CKD; however, it also lacked concurrent ascertainment of imaging and cognition. Other notable work originates from the Health, Aging, and Body Composition Study (Health ABC), where Kurella Tamura et al noted poorer baseline performance on the 3MS examination as well as a steeper decline in performance on this test over 4 years among those elderly individuals with lower estimated GFR levels as compared to those with estimated GFR of at least 60 mL/min/1.73 m^2.[26] Lastly, cross-sectional investigations using National Health and Nutrition Examination Survey (NHANES) 1999-2002 data have evaluated the association between cognitive performance and kidney disease. In one report of NHANES 1999-2002 participants, microalbuminuria, defined by urine albumin-creatinine ratio of 30 to 300 mg/g was independently associated with poorer performance on the 2-minute Digit Symbol Substitution Test (DSST), but only in the setting of peripheral arterial disease.[27] In a second study, worse cognitive performance was noted among 39 NHANES III participants between the ages of 20 and 59 years with estimated GFR below 60 mL/min/1.73 m^2 than among participants with intact kidney function of similar age.[28] This NHANES III study is limited by a very small sample size with CKD.

CLINICAL IMPLICATIONS OF THE COGNITION–KIDNEY DISEASE CONNECTION

The findings in both of these population-based studies are important and likely broadly generalizable, considerably expanding upon the prior work in this field. Essentially, these studies mark individuals with CKD as being at high risk for prevalent cognitive impairment. The implications, both for screening for cognition impairment as well as for care of individuals with CKD, are notable. For internists, neuropsychiatric specialists, and geriatricians, future prediction models could utilize albuminuria and reduced estimated GFR to help identify patients who could benefit from more detailed cognitive screening—a process that can take several hours per patient. For internists, nephrologists, and others caring for CKD patients, these studies raise awareness of an entirely new dimension of challenges. As management of chronic diseases becomes increasingly complex (for example, blood pressure and heart failure regimens routinely require 4 to 6 prescriptions), it is incumbent upon those caring for CKD patients to recognize that

these individuals may have difficulty with medication regimens and care plans—and that nonadherence may not be by choice but rather reflect the more intrinsic barrier of understanding their own medical care. Although future projects should assess the association of albuminuria and GFR with incident cognitive impairment and dementia, this research is an important first step in identifying how our patients manage, or rather fail to manage, the complexities of modern, pharmaceutical-intensive chronic medical care.

Daniel E. Weiner, MD, MS
Tufts Medical Center
Boston, Massachusetts

ACKNOWLEDGEMENTS

Support: None.
Financial Disclosure: None.

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