

# The brain and the kidney connection

## A model of accelerated vascular cognitive impairment



Anne M. Murray, MD,  
MSc

Address correspondence and  
reprint requests to Dr. Anne M.  
Murray, Chronic Disease  
Research Group, Minneapolis  
Medical Research Foundation,  
914 South 8th Street, Suite  
S-406, Minneapolis, MN 55404  
amurray@cdrg.org

*Neurology*® 2009;73:916–917

Patients with chronic kidney disease (CKD) exhibit tremendously high levels of symptomatic and occult cerebrovascular disease and associated inflammatory factors, homocysteine, anemia, hypertension, and diabetes.<sup>1–4</sup> As these risk factors overshadow aging and nonvascular factors, patients with CKD represent a potential model of accelerated vascular cognitive impairment.<sup>4</sup>

The brain and kidneys may be considered end organs on parallel trajectories, subject to shared cardiovascular risk factors, with microvascular pathologic processes mediated by inflammatory and oxidative processes taking place in similar low-resistance vascular beds and endothelial structures.<sup>4,5</sup> Impaired endothelial function in the brain is manifested by defects in the blood-brain barrier and susceptibility to microinfarcts, lacunar infarcts, and white matter changes, and in the kidney by impaired glomerular filtration and secondary protein leakage, or proteinuria.<sup>5</sup> Independently, the renal toxic effects of uremia, calcium-phosphate, other metabolic disturbances, and a potential genetic predisposition to exaggerated inflammatory response<sup>6</sup> likely accelerate cognitive decline.

In this issue of *Neurology*®, Buchman et al.<sup>7</sup> begin to unravel the convoluted relation between renal and cognitive impairment. Recent studies have described a graded, cross-sectional association between estimated glomerular filtration rate (eGFR) or proteinuria (albumin/creatinine ratio >30 mcg/mg) and brief cognitive screening tests, tests of specific cognitive domains, or dementia.<sup>8–10</sup> Longitudinal analyses have measured the relation between eGFR and dementia, or incident cognitive decline on the Modified Mini-Mental State (3MS) examination.<sup>11,12</sup> None has measured the effect of eGFR on rate of cognitive decline globally, using a detailed cognitive battery, and within multiple cognitive domains.

In the Rush Memory and Aging Project ( $n = 886$  community-dwelling adults without dementia, mean age 80.6 years), lower eGFR or having CKD (eGFR <60 mL/min/1.73 m<sup>2</sup>) was associated with more

rapid rate of global cognitive decline over approximately 3.4 years. For each eGFR reduction of 15 mL/min/1.73 m<sup>2</sup>, or at eGFR 45 mL/min/1.73 m<sup>2</sup> (equivalent to about 1 SD), the increased rate of global cognitive decline had the approximate effect of 3 years of aging. Given the mean age of this cohort and the known acceleration of dementia incidence after age 75 years, the added effect of 3 years of aging represents substantial cognitive decline. Likewise, having CKD was equivalent to 75% of the effect of an *APOE4* allele on the rate of cognitive decline. Renal impairment was associated with impaired global cognitive function, measured by the summary *z* score of 19 cognitive tests, and with the specific cognitive domains of episodic memory, semantic memory (verbal category fluency), and working memory, but not with visuospatial function or processing speed.

In a previous analysis,<sup>12</sup> an eGFR less than 45 mL/min/1.73 m<sup>2</sup> was associated with an increased risk of a 5-point decline on the 3MS, or a score <80 (adjusted odds ratio 2.43, 95% confidence interval 1.38–4.29). Thus, this loss of approximately half of renal reserve may be a useful biomarker for increased risk of cognitive decline.

The fact that other studies have not consistently found eGFR to be associated with cognitive decline does not refute the authors' findings. It suggests that renal-associated cognitive impairment is more vascular in origin than neurodegenerative, and that the trajectory and domains of cognitive impairment may differ for each patient.

Buchman et al. point out that subclinical vascular disease appears to play a strong role in the pathophysiology of cognitive impairment in patients with CKD. Cystatin C (a novel and perhaps more reliable measure of renal function) and lower eGFR are associated with silent stroke.<sup>1,13</sup> Prevalence of silent infarcts increases with CKD stage; systolic blood pressure >140 mm Hg multiplies this risk by 1- to 2-fold.<sup>1</sup> Not surprisingly, clinically evident stroke is more common as CKD advances; incidence is as

See page 920

*e-Pub ahead of print on August 19, 2009, at www.neurology.org.*

From the Department of Medicine and Geriatrics, Hennepin County Medical Center, Minneapolis, and Chronic Disease Research Group, Minneapolis Medical Research Foundation, MN.

*Disclosure:* Author disclosures are provided at the end of the editorial.

high as 15% per year for hemodialysis patients, vs 2.5% in the general Medicare population.<sup>2</sup> Brain imaging studies in CKD and dialysis patients report high rates of white matter disease and atrophy. In the Rotterdam Study, lower eGFR was significantly associated with brain atrophy and deep white matter lesion volume, and inversely associated with total white matter volume, but unrelated to gray matter volume on fully adjusted analyses.<sup>3</sup>

Most of the patients with CKD in the Rush Memory and Aging Project had relatively early and mild CKD (mean eGFR, 59 mL/min/1.73 m<sup>2</sup>), and only 29 patients (3.5%) had advanced CKD (eGFR <30 mL/min/1.73 m<sup>2</sup>). Thus, results may not generalize to patients with advanced CKD. Further, knowing the degree to which renal function covaries with cognitive function over time would be important.

For now, we need to practice preventive neurology<sup>14</sup> by screening younger patients for cardiovascular risk factors, all older patients for CKD with measures of serum creatinine and urine albumin/creatinine ratio, and patients with known CKD for cognitive impairment. If a patient's renal function is reduced by more than half, cognitive reserve is also likely depleted and should be assessed. Finally, patients with CKD should be targeted for aggressive stroke prevention.

#### DISCLOSURE

Dr. Murray receives research support from the NIH [NIA/NHLBI NO1-HC-95183 (Co-investigator; PI of the MN/IA Network), NIDDK NO1-DK-7-5002 (Co-investigator), and NIA 5 K23 AG021174-01A2 (PI)], from the Fesler-Lampert Chair in Aging at the University of Minnesota, and the Minneapolis Medical Research Foundation, and holds stock in Medtronic Inc.

#### REFERENCES

1. Kobayashi M, Hirawa N, Yatsu K, et al. Relationship between silent brain infarction and chronic kidney disease. *Nephrol Dial Transplant* 2009;24:201–207.
2. US Renal Data System. USRDS 2006 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2006.
3. Ikram MA, Vernooij MW, Hofman A, Niessen WJ, van der LA, Breteler MM. Kidney function is related to cerebral small vessel disease. *Stroke* 2008;39:55–61.
4. Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Adv Chronic Kidney Dis* 2008;15:123–132.
5. Seliger SL, Longstreth WT, Jr. Lessons about brain vascular disease from another pulsating organ, the kidney. *Stroke* 2008;39:5–6.
6. Stenvinkel P, Pecoits-Filho R, Lindholm B. Gene polymorphism association studies in dialysis: the nutrition-inflammation axis. *Semin Dial* 2005;18:322–330.
7. Buchman AS, Tanne D, Boyle PA, Shah RC, Leurgans SE, Bennett DA. Kidney function is associated with the rate of cognitive decline in the elderly. *Neurology* 2009;73:920–927.
8. Barzilay JI, Fitzpatrick AL, Luchsinger J, et al. Albuminuria and dementia in the elderly: a community study. *Am J Kidney Dis* 2008;52:216–226.
9. Kurella TM, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Kidney Dis* 2008;52:227–234.
10. Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, Robbins MA. Chronic kidney disease, creatinine and cognitive functioning. *Nephrol Dial Transplant* 2009;24:2446–2452.
11. Seliger SL, Siscovick DS, Stehman-Breen CO, et al. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. *J Am Soc Nephrol* 2004;15:1904–1911.
12. Kurella M, Chertow GM, Fried LF, et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *J Am Soc Nephrol* 2005;16:2127–2133.
13. Seliger SL, Longstreth WT, Jr., Katz R, et al. Cystatin C and subclinical brain infarction. *J Am Soc Nephrol* 2005;16:3721–3727.
14. Kivipelto M, Solomon A. Preventive neurology: on the way from knowledge to action. *Neurology* 2009;73:168–169.

# Neurology®

## The brain and the kidney connection: A model of accelerated vascular cognitive impairment

Anne M. Murray

*Neurology* 2009;73:916-917 Published Online before print August 19, 2009  
DOI 10.1212/WNL.0b013e3181b99a2e

**This information is current as of August 19, 2009**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://www.neurology.org/content/73/12/916.full.html">http://www.neurology.org/content/73/12/916.full.html</a>
<b>References</b>	This article cites 13 articles, 9 of which you can access for free at: <a href="http://www.neurology.org/content/73/12/916.full.html##ref-list-1">http://www.neurology.org/content/73/12/916.full.html##ref-list-1</a>
<b>Citations</b>	This article has been cited by 2 HighWire-hosted articles: <a href="http://www.neurology.org/content/73/12/916.full.html##otherarticles">http://www.neurology.org/content/73/12/916.full.html##otherarticles</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>All Cognitive Disorders/Dementia</b> <a href="http://www.neurology.org/cgi/collection/all_cognitive_disorders_dementia">http://www.neurology.org/cgi/collection/all_cognitive_disorders_dementia</a> <b>Cognitive aging</b> <a href="http://www.neurology.org/cgi/collection/cognitive_aging">http://www.neurology.org/cgi/collection/cognitive_aging</a> <b>Cohort studies</b> <a href="http://www.neurology.org/cgi/collection/cohort_studies">http://www.neurology.org/cgi/collection/cohort_studies</a> <b>Risk factors in epidemiology</b> <a href="http://www.neurology.org/cgi/collection/risk_factors_in_epidemiology">http://www.neurology.org/cgi/collection/risk_factors_in_epidemiology</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: <a href="http://www.neurology.org/misc/about.xhtml#permissions">http://www.neurology.org/misc/about.xhtml#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.neurology.org/misc/addir.xhtml#reprintsus">http://www.neurology.org/misc/addir.xhtml#reprintsus</a>

*Neurology*® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

