Cognitive Disorders and Dementia in CKD: The Neglected Kidney-Brain Axis

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ABSTRACT

Epidemiologic data suggest that individuals at all stages of CKD have a higher risk of developing cognitive disorders and dementia. This risk is generally explained by the high prevalence of both symptomatic and subclinical ischemic cerebrovascular lesions. However, other potential mechanisms, including direct neuronal injury by uremic toxins, could also be involved, especially in the absence of obvious cerebrovascular disease. We discuss the prevalence and characteristics of cognitive disorders and dementia in patients with CKD, brain imaging findings, and traditional and nontraditional risk factors. Understanding the pathophysiologic interactions between renal impairment and brain function is important in order to minimize the risk for future cognitive impairment.


CKD is a substantial public health problem. On the basis of the French national renal data system, it has been estimated that between 1.75 and 2.5 million people in France have CKD1 and that nearly 40,000 of the latter are undergoing dialysis. In the United States, similar results have been observed: Almost 8% of the population has CKD and 571,000 patients receive treatment for ESRD.2 Although the incidence of CKD is increasing in all age groups, this is particularly true in the elderly.3 Older adults are at a greater risk of developing cognitive disorders and dementia, and a major determinant of the quality of life in the elderly is the level of cognitive function.4 Recent data in this regard suggest that individuals at all stages of CKD may have a higher risk of developing dementia and cognitive impairment than those without CKD.5–7 Given the increase in life expectancy and the aging of the population in industrialized countries, the cognitive disorder burden associated with CKD is expected to worsen.

PREVALENCE AND CHARACTERISTICS OF COGNITIVE IMPAIRMENT IN CKD

Patients with Stage 5 CKD

In hemodialysis patients, the prevalence of cognitive impairment has been estimated at 30%–60%6,8–10—at least twice the values observed in age-matched controls.11 Table 1 summarizes the characteristics of the main studies assessing the prevalence of cognitive impairment in hemodialysis patients. One main limitation of these early studies concerns the cognitive assessment. Initially, cognitive impairment was based on short screening tests, such as the Mini-Mental State Examination (MMSE)12 and the 3MS (an extension of the MMSE with four additional subtests and a maximum score of 100 points instead of 30 points). The limited sensitivity of short screening tests of cognitive impairment in general and vascular cognitive impairment in particular13 probably led to an underestimation of the prevalence of cognitive impairment in CKD. In a cross-sectional study, Murray et al. compared 338 hemodialysis patients age 55 years and older with age-matched controls.14 Although only 3% of the patients had a documented history of cognitive impairment, further neuropsychological testing showed that the true prevalence of mild to severe cognitive impairment was as high as 87%. This finding was emphasized by another study by Kurella et al.15 According to data collected from a large, international sample of hemodialysis patients with a mean age of 60, only 4% of patients had a previously documented diagnosis of dementia. This value is lower than the prevalence reported in the general population age 65 or older.16,17

Another important limitation in the interpretation of study data concerns study design, which differs from one study to the other. Some investigators did not report the proportion of

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Table 1. Prevalence of cognitive disorders and dementia in hemodialysis patients

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Mean Age (yr)</th>
<th>Assessment</th>
<th>Cognitive Tests</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fazekas et al., 1995 (case-control study)</td>
<td>60 patients ≥ 35 yr (30 hemodialysis patients vs. 30 healthy controls)</td>
<td>58</td>
<td>During dialysis</td>
<td>General screening test (MMSE, MDRS)</td>
<td>Mean MMSE score = 22.9 (vs. 27.9; P &lt; 0.001)</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Sehgal et al., 1997 (observational study; 3 centers)</td>
<td>336 patients ≥ 18 yr</td>
<td>59</td>
<td>During dialysis</td>
<td>MMSE: Mild cognitive impairment: MMSE ≤ 23</td>
<td>Mean MMSE score = 20.7</td>
<td>Comorbid conditions and educational and functional status not taken into account</td>
</tr>
<tr>
<td>Antoine et al., 2004 (observational study; 1 center)</td>
<td>33 patients ≥ 75 yr</td>
<td>80</td>
<td>During dialysis</td>
<td>MMSE: Cognitive impairment: MMSE &lt; 24</td>
<td>Mean MMSE score = 25.7</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Kurella et al., 2004 (cross-sectional study)</td>
<td>80 hemodialysis patients ≥ 20 yr</td>
<td>61</td>
<td>During dialysis</td>
<td>3 tests: global cognitive function (3MS), executive functions (TMT B), and immediate and delayed verbal memory (CVLT)</td>
<td>Cognitive impairment if: 3MS &lt; 30 s; TMT B = 300 s in 38% of patients; CVLT: abnormal score in ≥ 33% of patients</td>
<td>No established cut-offs for CVLT, small sample size</td>
</tr>
<tr>
<td>Kurella et al., 2006 (DOPPS) (cohort study)</td>
<td>16,694 patients</td>
<td>60</td>
<td>—</td>
<td>Dementia noted in the medical records</td>
<td>4% with dementia in the entire cohort</td>
<td>Cross-sectional study, diagnostic of dementia based on review of medical records (underestimation?)</td>
</tr>
<tr>
<td>Murray et al., 2006 (cross-sectional study)</td>
<td>338 patients ≥ 55 yr</td>
<td>71</td>
<td>Before, during, or after hemodialysis (&lt; 1 h)</td>
<td>Neuropsychological battery with 9 tests for 3 domains (memory, executive functions, and language); cognitive impairment algorithm: Normal: scored ≤ 1.49 SDs below the age-adjusted mean on all tests in all domains</td>
<td>Cognitive impairment in 87% of patients: Mild cognitive impairment: 14%; Moderate cognitive impairment: 56%; Severe cognitive impairment: 37%</td>
<td>Absence of education and ethnicity-based norms for all neuropsychological tests, low participation rate</td>
</tr>
</tbody>
</table>

DSM III-R: Diagnostic and Statistical Manual of Mental Disorders III-Revised; MDRS, Mattis Dementia Rating Scale; 3MS, Modified Mini Mental Test Examination; TMT B, Trail-making Test part B; CVLT, California Verbal Learning Test; DOPPS, Dialysis Outcomes and Practice Patterns Study; RR, relative risk.
Cognitive Disorders in CKD Patients

BRIEF REVIEW

Brain Lesions in CKD Patients

Brain lesions in CKD patients were first described in computed tomography–based studies (Table 3). More than 30 years ago, Passer et al. reported a high prevalence of cerebral atrophy in patients undergoing long-term hemodialysis.32 It was subsequently shown in such patients that the lesions were prominent in the frontal lobes and were correlated with the duration of hemodialysis.33,34 Other markers or risk factors for potential cerebrovascular disease, such as SBIs, have also been reported. Cusmano and Savazzi showed that 10% of CKD patients, most of whom were undergoing hemodialysis, had SBIs.35 More recently, we found a strong association between eGFR and intracranial artery calcification in patients hospitalized for stroke or nonvascular neurologic disorders.36 This is not surprising, given that CKD is associated with an accelerated, active vascular calcification process.37

Magnetic resonance imaging (MRI) has allowed a considerable increase in the rate of detection of subclinical cerebrovascular damage in CKD patients. It has been estimated that approximately half of the patients with advanced CKD stages have SBIs, whereas the prevalence in the general population ranges from 8% to 28%.38 SBIs are associated with an increased risk for stroke, cognitive decline, and incident dementia in CKD patients.39 Furthermore, a small prospective cohort study showed that SBIs were an independent prognostic factor for the progression of kidney disease in patients.
Table 2. Main studies of association between mild to moderate CKD and cognitive impairment

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Cognitive Tests</th>
<th>Renal Function Assessment</th>
<th>Results</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Kurella et al., 2004&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Cross-sectional study</td>
<td>80 hemodialysis patients and 80 CKD patients ≥20 yr Mean age, 63 yr</td>
<td>3 tests: 3MS, TMT B, and CVLT Cognitive impairment if: 3MS score &lt; 80 TMT B = 300 s CVLT: recall of &lt; 4 words or more than 2 SDs from mean CVLT score MDRD (6 items)</td>
<td>Graded relation between cognitive function and severity of CKD In hemodialysis patients: see Table 1 In CKD patients: 3MS score &lt; 80 in 15% of patients TMT B = 300 s in 23% of patients CVLT: abnormal score in 28% of patients</td>
<td>No control group (results compared with published norms) No established cutoffs for CVLT</td>
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<td>Seliger et al., 2004&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Cohort study</td>
<td>Population of community-dwelling older adults free of dementia at baseline 3349 patients ≥ 65 yr Median follow-up, 6 yr Mean age, 75 yr</td>
<td>Neuropsychological testing (including the American version of the national reading test, Raven colored progressive matrices, CVLT, Rey-Osterreith figure, immediate and delayed recall, modified Boston naming test, verbal fluency, Stroop test, TMT, digit spans, Baddeley and Papagno divided attention task) Diagnosis of dementia according to the DSM III-R criteria Moderate renal impairment defined as: SCr ≥ 1.3 mg/dl for women ″ SCr ≥ 1.5 mg/dl for men</td>
<td>Moderate renal impairment associated with 37% increased risk for dementia (95% CI, 1.06–1.78)</td>
<td>Cases of incident dementia were identified retrospectively Renal function at baseline assessed by reciprocal of SCr (1/SCr)</td>
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<td>Kurella et al., 2005&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Cross-sectional study</td>
<td>1015 women &lt; 80 yr with established coronary artery disease Mean age, 67 yr</td>
<td>3MS (cognitive impairment if 3MS score &lt; 80)</td>
<td>MDRD (6 items)</td>
<td>Risk for global cognitive impairment was increased 5-fold in women with eGFR &lt; 30 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt; eGFR was significantly associated with global cognitive impairment, executive function, language, and memory (15%–25% increase in risk for dysfunction/10-mL/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt; decrement in eGFR)</td>
<td>Selected population Hemoglobin and hematocrit values not collected</td>
</tr>
<tr>
<td>Kurella et al., 2005&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Longitudinal study</td>
<td>3034 community-dwelling older adults Mean age, 74 yr</td>
<td>3MS (at baseline and at 2 and 4 yr of follow-up) Cognitive impairment defined as 3MS score &lt; 80 or decline in 3MS &gt; 5 points after 2 or 4 yr of follow-up among participants with baseline 3MS scores &gt; 80 MDRD (4 items)</td>
<td>CKD defined as eGFR &lt; 60 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Lower baseline eGFR is associated with cognitive impairment CKD is associated with increased risk (36%) for cognitive impairment OR, 1.32 (eGFR 45–59 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;) OR, 2.43 (eGFR &lt; 45 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>Only 1 measurement of serum creatinine (at baseline)</td>
</tr>
<tr>
<td>Hailem et al., 200&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Cross-sectional study</td>
<td>4849 young healthy adults (age 20–59 yr) Mean age, 36 yr</td>
<td>Visual motor reaction time Visual attention Learning/concentration</td>
<td>MDRD (4 items)</td>
<td>Moderate CKD defined as eGFR 30–49 ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>OR, 2.41 Impairment in visual attention (OR, 2.74)</td>
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</table>

Hailpern et al., 200<sup>7</sup> (NHANES III)
Table 2. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Cognitive Tests</th>
<th>Renal Function Assessment</th>
<th>Results</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Kurella Tamura et al., 2008</td>
<td>Cross-sectional study</td>
<td>23405 patients ≥ 45 yr Mean age, 65 yr</td>
<td>6-item cognitive screening examination</td>
<td>MDRD (4 items)</td>
<td>11% of patients had CKD and 8% had cognitive impairment</td>
<td>Insensitive measurement of cognitive function</td>
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<td>(REGARDS)</td>
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<td>Cognitive impairment defined as score ≤ 4</td>
<td>CKD defined as eGFR &lt; 60 ml/min per 1.73 m²</td>
<td>CKD was associated with increased prevalence of cognitive impairment (OR, 1.23)</td>
<td>Cognitive assessment by telephone interview</td>
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<td>Slinin et al., 2008</td>
<td>Observational prospective study</td>
<td>5529 community-dwelling men ≥ 65 yr Mean follow-up, 5 yr Mean age, 74 yr</td>
<td>3MS (cognitive impairment defined as 3MS &lt; 80)</td>
<td>MDRD (4 items)</td>
<td>3 MS score &lt; 80 in 15% of patients, TMT B=300 s in 23% of patients</td>
<td>Limited neuropsychological tests</td>
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<td>(MrOS)</td>
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<td>TMT B (cognitive impairment defined as TMT B time &gt;1.5 SDs above the mean)</td>
<td>3 eGFR groups (ml/min per 1.73 m²):</td>
<td>Association between worse renal function and higher odds of impairment based on TMT B test score at baseline</td>
<td>Healthy participant population</td>
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<td>eGFR &gt; 60</td>
<td>No association between eGFR and cognitive decline during the follow-up</td>
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<td>eGFR&lt;60</td>
<td>At baseline, 11% had cognitive impairment</td>
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<td>eGFR&lt;45</td>
<td>After 2-yr follow-up: 6.2% patients with new cognitive impairment:</td>
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<td>No CKD: 5.8%</td>
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<td>Mild CKD: 9.9%</td>
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<td>Moderate CKD: 21.5%</td>
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<td></td>
<td>Patients with moderate to severe kidney disease at baseline were at high risk of developing new cognitive impairment after 2-yr follow-up (OR, 2.14)</td>
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<td>Etgen et al., 2009</td>
<td>Cohort study</td>
<td>3679 community-dwelling adults 2-yr follow-up Mean age, 68 yr</td>
<td>6-CIT (6 questions: asking for the year, month, and time; counting backward from 20 to 1; saying the months of the year in reverse order; remembering an address with five components) Cognitive impairment defined as a score &gt; 7</td>
<td>Cockcroft-Gault equation for eGFR (ml/min per 1.73 m²):</td>
<td>Participants with lower eGFR had lower cognitive scores on most cognitive domains</td>
<td>No association between CKD and cognitive impairment with use of MDRD equation</td>
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<td>(INVADE)</td>
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<td>≥60: normal</td>
<td>No CKD: 5.8%</td>
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<td>45–59: mild</td>
<td>Mild CKD: 9.9%</td>
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<td>&lt;45: moderate</td>
<td>Moderate CKD: 21.5%</td>
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<td>Patients with moderate to severe kidney disease at baseline were at high risk of developing new cognitive impairment after 2-yr follow-up (OR, 2.14)</td>
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<tr>
<td>Yaffe et al., 2010</td>
<td>Cross-sectional study</td>
<td>825 CKD patients Age ≥ 55 yr</td>
<td>Global cognition</td>
<td>MDRD (4 items)</td>
<td>Participants with lower eGFR had lower cognitive scores on most cognitive domains</td>
<td>MDRD equation not validated in nonwhite populations (45% of patients were black)</td>
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<tr>
<td>(CRICS)</td>
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<td>Naming</td>
<td>Advanced CKD: eGFR = 45–59 ml/min per 1.73 m²</td>
<td>Participants with advanced CKD were more likely to have clinically significant cognitive impairment on most cognitive domains than those with mild to moderate CKD</td>
<td>Small sample of patients without CKD (n=80)</td>
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<td>Attention</td>
<td>Mild to moderate CKD: eGFR &lt; 30 ml/min per 1.73 m²</td>
<td>CCKD at baseline was associated with faster rate of cognitive decline</td>
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<td>Executive functions</td>
<td></td>
<td>CCKD associated with altered semantic memory, episodic memory, and working memory but not visuospatial abilities or perceptual speed</td>
<td>No measure of inflammatory markers Selected (older) patients</td>
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<td>Memory delayed</td>
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<td>Category fluency</td>
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<tr>
<td>Buchman et al., 2009</td>
<td>Observational cohort study</td>
<td>886 community-dwelling elderly adults without dementia, followed up for 3.4 yr Mean age, 81 years</td>
<td>Neuropsychological tests performed at baseline and annually: MMSE 19 tests for 5 domains (semantic memory, episodic memory, working memory, visuospatial abilities, and perceptual speed)</td>
<td>MDRD (4 items)</td>
<td>Patients with lower eGFR had lower cognitive scores on most cognitive domains</td>
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<td>(RMAP)</td>
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<td>CKD defined as eGFR &lt; 60 ml/min per 1.73 m²</td>
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</table>

3MS, Modified Mini-Mental State Examination; TMT B, Trailmaking Test part B; CVLT, California Verbal Learning Trial; MDRD, Modification of Diet in Renal Disease; CHCS, Cardiovascular Health Cognition Study; DSM IV-R, Diagnostic and Statistical Manual of Mental Disorders IV- Revised; SCr, serum creatine; CI, confidence interval; HERS, Heart Estrogen/Progestin Replacement Study; HABCS, Health, Aging and Body Composition Study; NHANES III: Third National Health and Nutrition Examination Survey; OR, odds ratio; REGARDS, Reasons for Geographic and Racial Differences in Stroke Study; MrOS, Osteoporotic fractures in Men; INVADE, Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg; 6-CIT, 6-Item Cognitive Impairment test; CRICS, Chronic Renal Insufficiency Cohort Study; RMAP, Rush Memory and Aging Project.
Likewise, the prevalence of WMLs is high (up to 70%) in both CKD patients and stroke patients. This is not surprising, given that WMLs are thought to be symptomatic of a progressive, irreversible process that follows on from arteriolosclerosis. Most cross-sectional, population-based studies show a strong association between eGFR on one hand and white matter volume and WMLs on the other. Only Martinez-Vea et al. failed to report a statistically significant relationship between vascular nephropathy and WMLs in a multivariate analysis. This absence suggests that the elevated number of WMLs in CKD patients is a marker of systemic vascular disease. As with SBIs, WMLs are predictors of an increased incidence of stroke, dementia, and death. Other markers strongly associated with cerebral small vessel disease (microbleeds or microhemorrhages) have been studied less extensively.

The incidence of cerebral microbleeds is higher in patients undergoing hemodialysis and also in patients with a more moderate decrease in renal function. In two other studies performed in patients with ischemic stroke, similar associations between chemical markers of CKD and cerebral microbleeds have been observed. Interestingly, Watanabe also found a high incidence of microbleeds in patients undergoing maintenance hemodialysis but failed to find any correlation between the duration of hemodialysis and the prevalence of microbleeds. The author concluded that the high proportion of patients with microbleeds in this population was caused by other risk factors, possibly arterial hypertension and uremic toxins, rather than maintenance hemodialysis per se. However, one must bear in mind that most of the above studies were performed in Asian persons—an ethnic group whose patterns of clinically evident and subclinical cerebrovascular disease greatly differs from that in other populations. This point was recently emphasized by the results of a meta-analysis by Lee et al. in which the presence of low eGFR was a marker for increased risk for stroke, with the highest risk being observed in Asian populations.

**POTENTIAL CAUSES OF COGNITIVE IMPAIRMENT IN PATIENTS WITH CKD**

**The Vascular Hypothesis of Cognitive Impairment**

Figure 2 presents the possible causes of cognitive impairment in patients with CKD. The brain and the kidneys have many common anatomic and vasoregulatory features; they are low resistance end organs exposed to high-volume blood flow and thus are susceptible to vascular damage. Hence, impaired cerebral hemodynamics, as evaluated by transcranial Doppler ultrasonography, may reveal interesting information on the association between altered cerebrovascular hemodynamics and cognitive impairment. Indeed, previous transcranial Doppler studies show a positive correlation between hemodynamic impairment and cognitive impairment—suggesting that microvascular damage contributes to the cognitive changes observed in the early stages of dementia. Additionally, the prevalence of traditional

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**Figure 1.** Subclinical brain lesions in CKD patients. (A) Axial fluid-attenuated inversion recovery magnetic resonance image showing silent brain lacunar infarct (arrow). (B) Axial gradient-echo magnetic resonance imaging sequence showing multiple microbleeds (small foci of hypointensity, arrows) located in the right cerebral hemisphere. Moderate (C) and severe (D) white-matter lesions in the centrum ovale.
Table 3. Main brain imaging studies in CKD patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Renal Function Assessment</th>
<th>Imaging</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fazekas et al., 1995⁹</td>
<td>Cross-sectional study</td>
<td>60 hemodialysis patients age ≥ 35 yr Mean age, 58 yr</td>
<td>On dialysis</td>
<td>MRI 1.5 T</td>
<td>CKD associated with:</td>
<td>Small sample size</td>
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<tr>
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<td>Cortical atrophy (50%)</td>
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<td>White matter hyperintensities (80%)</td>
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<td>Ischemic abnormalities (63%)</td>
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<tr>
<td>Seliger et al., 2005⁸</td>
<td>Cross-sectional study</td>
<td>2784 elderly (≥ 65 yr)</td>
<td>Serum creatine and cystatin-C</td>
<td>MRI 1.5 T</td>
<td>SBI defined as infarct-like lesion ≤ 3 mm in participant without previous stroke or TIA</td>
<td>Cross-sectional design</td>
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<td>SBI was present in 789 patients (28%)</td>
<td>CHS participants who completed cranial MRI were healthier than those who did not</td>
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<td>Prevalence of SBI was directly associated with quintile of cystatin-C, whereas association with SCf and SBI was U-shaped</td>
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<tr>
<td>Yokoyama et al., 2005⁴⁵</td>
<td>Cross-sectional study</td>
<td>57 patients on hemodialysis</td>
<td>On dialysis</td>
<td>MRI 0.5 T Microbleeds defined as homogeneous rounded lesions with diameter of 2–5 mm on T2*–weighted gradient echo imaging</td>
<td>Microbleeds were present in 11 of 57 patients (19%)</td>
<td>Small sample size</td>
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<td>Ikram et al., 2008⁴⁴ (RSS)</td>
<td>Cross-sectional study</td>
<td>484 participants age ≥ 60 yr Mean age, 73 yr</td>
<td>Cockcroft-Gault equation</td>
<td>MRI 1.5 T Automated MRI analysis of lobar and deep volumes of gray matter and white matter, and volume of white matter lesions</td>
<td>Participants with lower GFR had smaller deep white matter volume, more white matter lesions GFR was not associated with gray matter volume or lobar white matter volume</td>
<td>Only 1 measurement of eGFR</td>
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<td></td>
<td>No distinction between lacunar infarcts and dilated perivascular spaces</td>
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<td>Kobayashi et al., 2009⁴⁶</td>
<td>Cross-sectional study</td>
<td>375 patients (335 CKD patients and 40 hypertensive patients) Mean age, 63 yr</td>
<td>MDRD formula CKD defined as eGFR &lt;60 ml/min per 1.73 m²</td>
<td>MRI 1.5 T SBI defined as focal area ≥ 3 mm and &lt;20 mm in diameter in both T1- and T2-weighted sequences</td>
<td>There was graded association between eGFR (ml/min per 1.73 m²) and SBIs: eGFR 30–59: OR, 1.34 (95% CI, 0.68–1.99) eGFR 15–29: OR, 1.94 (95% CI, 1.30–2.57) eGFR &lt;15: OR, 2.51 (95% CI, 1.91–3.10) (versus eGFR = 60 ml/min per 1.73 m²)</td>
<td>No healthy control group</td>
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<td>Khatri et al., 2007⁴⁵ (NOMAS)</td>
<td>Cross-sectional</td>
<td>615 community-based patients age ≥ 55 yr Mean age, 70 yr</td>
<td>MDRD formula, Cockcroft-Gault equation</td>
<td>MRI 1.5 T Quantitative analysis of white matter hyperintensities (log-white matter hyperintensity volume)</td>
<td>Association between moderate to severe CKD (eGFR 15–59 ml/min/1.73 m²) and white matter hyperintensities</td>
<td>MRI sample healthier than overall cohort</td>
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<tr>
<td>Cho et al., 2009⁵¹</td>
<td>Cross-sectional</td>
<td>152 ischemic stroke patients</td>
<td>MDRD equation (4 items)</td>
<td>MRI 1.5 T Assessment of cerebral microbleeds using gradient echo MRI Multisector CT</td>
<td>Hypertension, white matter lesions, old age, and low GFR (OR, 3.85) were associated with cerebral microbleeds</td>
<td>Small number of patients</td>
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<td>Population limited to ischemic stroke patients</td>
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<tr>
<td>Bugnicourt et al., 2009⁵⁴</td>
<td>Cross-sectional</td>
<td>Patients with neurologic disorders</td>
<td>MDRD formula</td>
<td>MRI 1.5 T SBI defined as focal area ≥ 3 mm and &lt;20 mm in diameter in both T1- and T2-weighted sequences</td>
<td>Association between intracranial artery calcification and eGFR Presence of SBI was independent predictor of study outcomes (HR, 2.16; 95% CI, 1.01–4.64; P = 0.04) eGFR decreased more in patients with SBIs than in those without SBIs</td>
<td>Study limited to population with neurologic disorders</td>
</tr>
<tr>
<td>Kobayashi et al., 2010⁶⁰</td>
<td>Prospective cohort study</td>
<td>142 CKD patients (stages 3–5) followed up for 2 yr</td>
<td>MDRD formula</td>
<td>MRI 1.5 T</td>
<td>Primary outcome was doubling of serum creatinine level, development of ESRD (defined as dialysis or transplant) and death from cardiovascular causes</td>
<td>Small sample size</td>
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</table>

TIA, transient ischemic attack; SCr, serum creatinine; CHS, Cardiovascular Health Study; RSS, Rotterdam Scan Study; MDRD, Modification of Diet in Renal Disease; OR, odds ratio, CI, confidence interval; NOMAS, Northern Manhattan Study; HR, hazard ratio.
vascular risk factors, such as arterial hy-
pertension, is higher in patients with CKD
than in the general population.² This
might explain the association between
CKD and cerebrovascular disease because
the latter plays the largest role in the path-
ogenesis of cognitive impairment in CKD
patients.

Furthermore, it has been suggested
that vascular disease is a more likely
cause of cognitive impairment than is Alz-
heimer’s disease in this population. This
hypothesis is supported by recent
published data from the 3C study: Faster
eGFR decline (>4 ml/min per 1.73 m²
during the first 4-year period of follow-
up) was associated with global cognitive
decline and incident dementia with a vas-
cular component.⁴⁹ The contribution of
cerebral vascular lesions to cognitive
impairment in CKD patients is also
supported by the pattern of cognitive
disorders; the prominent impairment
of executive functions and psycho-
motor speed resembles the situation
in stroke.⁵⁹ However, the results of a
neuropathologic study indicates that
patients with small-vessel cerebrovas-
cular disease present broader cognitive
impairment, which can also include
memory deficits. These findings thus
challenge the utility of executive impair-
ment as a diagnostic marker for vascular
cognitive impairment or dementia.⁶⁰

Nontraditional vascular risk factors,
such as hyperhomocysteinemia, hyper-
coagulable states, inflammation, and ox-
idative stress, have also been linked to
cognitive impairment.⁶¹ These factors
could accelerate the progression of ath-
erosclerosis and vascular endothelial dys-
function, both of which are associated
with dementia risk.⁶²,⁶³ Interestingly, el-
evated homocysteine levels are present
in 85% of dialysis patients but only
10% of the general population.⁶⁴ In a
prospective cohort study, plasma homo-
cysteine was an independent risk factor
for dementia.⁶⁵

There are several possible mechanisms
through which elevated homocysteine
levels may cause cognitive impairment.
First, hyperhomocysteinemia has a direct
prothrombotic effect on the vascular
system and thus may lead to both large-
and small-vessel disease.⁶⁶ Elevated ho-
mocysteine levels are also associated with
the number of WMLs and progression—
possibly through direct endothelial
damage or stimulation of an endothelial
inflammatory response.⁶⁵,⁶⁷,⁶⁸ Second, hyperhomocysteinemia could impair
neuronal pathways because elevated ho-
mocysteine has a direct, neurotoxic effect
by activating the N-methyl-D-aspartate
receptor or by conversion into homocys-
teic acid, leading to cell death.⁶⁹ Further-
more, clinical studies show that elevated
plasma homocysteine concentrations are
associated with an increased risk for Alz-
heimer disease.⁷⁰ However, lowering ho-
mocysteine levels in dementia patients
does not appear to reduce global cognitive
decline.⁷¹

The Neurodegenerative Hypothesis
of Cognitive Impairment

The vascular risk factors and brain ab-
normalities mentioned above can only
partly explain the high frequency of
vasculopathy-related cognitive disorders
observed in CKD patients. Hence, other
disease mechanisms are necessarily in-
volved. First, chronic hypertension and
numerous vascular risk factors are associ-
ated with an increased risk for Alzheimer
disease.⁷² Conversely, the results of obser-
vational studies and clinical trials suggest
that antihypertensive drugs may decrease
age-related cognitive decline and demen-
tia, although longitudinal studies have
provided inconsistent findings.⁷³ In
2001, the Rotterdam study showed that
antihypertensive treatment was associated
only with a lower risk for vascular demen-
tia.⁷⁴ However, the Systolic Hypertension
in Europe (Syst-Eur) and Syst-Eur 2 trials
showed a significant, 50% reduction in
the incidence of both vascular and neuro-
degenerative dementia.⁷⁵,⁷⁶ During the
past decade, most studies have focused
on the observation that beneficial effects
of various antihypertensive drugs in pre-
venting cognitive decline and dementia
are apparently not correlated with their
BP-lowering activity.⁷⁷

It has been suggested that angiotensin-
converting enzyme inhibitors might have
deleterious effects on cognition (because

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**Figure 2.** Schematic representation of potential causes of cognitive impairment in patients with CKD.

they prevent angiotensin-converting enzyme–mediated conversion of AB42 into AB10, which is less amyloidogenic and less toxic), whereas angiotensin AT1-receptor blockers might exert a protective effect on cognition due to their activation of AT2 and AT4 receptors. Moreover, the accumulation of uremic toxins may cause cerebral endothelial dysfunction and contribute to cognitive disorders in CKD. Various uremic toxins have been implicated in the pathogenesis of cognitive impairment. DeDeyn et al. reported that cerebrospinal fluid and brain levels of some guanidine compounds, such as creatinine, guanidine, guanidinosuccinic acid, and methylguanidine, are substantially elevated in uremic patients. Interestingly, these high toxin concentrations (up to 10-fold higher in CKD patients than in controls) were found in brain regions that play a determinant role in cognition, such as the thalamus, the mammillary bodies, and the cerebral cortex. It is well known that these uremic guanidine compounds are neuroexcitatory agents and have convulsant activity in animal studies. However, it is still not clear whether uremic toxins are directly responsible for cognitive impairment. The involvement of guanidines in cognitive disorders could also be indirect because it has been shown that these compounds favor an elevation of serum homocysteine. Lastly, Yaffe et al. showed that community-resident elderly individuals with elevated levels of cystatin-C (an inhibitor of cysteine proteases that co-localizes with β-amyloid in the brain of patients with Alzheimer disease) had lower cognitive test scores and were more likely to experience a decline in cognitive function during a 7-year follow-up period—even after adjustment for vascular risk factors. Despite the absence of brain MRI data, it is possible that cystatin-C has a direct effect on the risk of developing Alzheimer disease. 

CONCLUSION

The pathophysiologic link between brain and kidney injury is strong and complex. The cognitive disorders observed in CKD patients are probably explained by the common susceptibility of brain tissue to vascular injury. Brain MRI should be systematically performed in CKD patients with cognitive impairment because the frequency of both clinically apparent and silent cerebrovascular lesions is strikingly increased compared with that in the general population. In addition to cerebrovascular causes, other potential mechanisms, such as direct neuronal toxicity of the uremic state, could also be involved in CKD patients with cognitive disorders, especially in the absence of obvious cerebrovascular disease. Understanding the pathophysiologic interactions between renal impairment and brain function in CKD patients is important in order to minimize the risk for future cognitive impairment. Attempt to reach this goal would benefit from collaboration between neurologists and nephrologists.

DISCLOSURES.

None.

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