

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.

J Am Soc Nephrol 24: 353–363, 2013. doi: 10.1681/ASN.2012050536

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

Published online ahead of print. Publication date available at www.jasn.org.

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

Study Design	Population	Mean Age (yr)	Assessment	Cognitive Tests	Results	Limitations
Fazekas et al., 1995 ⁹ (case-control study)	60 patients \geq 35 yr (30 hemodialysis patients vs. 30 healthy controls)	58	During dialysis	General screening test (MMSE, MDRS) diagnosis of dementia according to the DSM III-R criteria	Mean MMSE score = 22.9 (vs. 27.9; $P < 0.001$) 80% of patients with dementia 60% of patients with abnormal results in both global cognitive tests	Small sample size
Sehgal et al., 1997 ¹⁰ (observational study; 3 centers)	336 patients \geq 18 yr	59	During dialysis	MMSE: Mild cognitive impairment: 18 \leq MMSE \leq 23 Severe cognitive impairment: MMSE \leq 17	Mean MMSE score = 20.7 Mild cognitive impairment: 22% Severe cognitive impairment: 8%	Comorbid conditions and educational and functional status not taken into account Small sample size
Antoine et al., 2004 ⁸ (observational study; 1 center)	33 patients \geq 75 yr	80	During dialysis	MMSE: Cognitive impairment: MMSE $<$ 24	Mean MMSE score = 25.7 Cognitive impairment in 24% of participants	
Kurella et al., 2004 ⁶ (cross-sectional study)	80 hemodialysis patients \geq 20 yr	61	During dialysis	3 tests: global cognitive function (3MS), executive functions (TMT B), and immediate and delayed verbal memory (CVLT) Cognitive impairment if: 3MS $<$ 80 TMT B = 300 s CVLT: recall of $<$ 4 words or more than 2 SDs from the mean CVLT score	In hemodialysis patients: 3MS $<$ 80 in 27% of patients TMT B = 300 s in 38% of patients CVLT: abnormal score in 33% of patients	No established cut-offs for CVLT, small sample size
Kurella et al., 2006 ¹⁵ (DOPPS) (cohort study)	16,694 patients	60	—	Dementia noted in the medical records	4% with dementia in the entire cohort Risk factors for dementia were age, black race, low education level, cerebrovascular disease, and diabetes Dementia significantly associated with increased risk for death (RR, 1.48) and dialysis withdrawal (RR, 2.01)	Cross-sectional study, diagnostic of dementia based on review of medical records (underestimation?)
Murray et al., 2006 ¹⁴ (cross-sectional study)	338 patients \geq 55 yr	71	Before, during, or after hemodialysis ($<$ 1 h)	Neuropsychological battery with 9 tests for 3 domains (memory, executive functions and language), cognitive impairment algorithm: Normal: scored \leq 1.49 SDs below the age-adjusted mean on all tests in all domains Mild cognitive impairment: scored 1.50–1.99 SDs below the age-adjusted mean in \leq 1 domain Moderate cognitive impairment: scored 1.50–1.99 SDs below the age-adjusted mean on \geq 1 tests in $>$ 1 domain, or \geq 2.00 SDs below the mean in \leq 1 domain Severe cognitive impairment: scored \geq 2.00 SDs below the age-adjusted mean on \geq 1 in \geq 2 domains	Cognitive impairment in 87% of patients: Mild cognitive impairment: 14% Moderate cognitive impairment: 36% Severe cognitive impairment: 37%	Absence of education and ethnicity-based norms for all neuropsychological tests, low participation rate

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 Trial; DOPPS: Dialysis Outcomes and Practice Patterns Study; RR, relative risk.

nonevaluated patients or provide information on confounding factors, such as sociocultural demographic characteristics, the presence of depressive syndrome, vascular risk factors, and prior cerebrovascular events (such as stroke).

Lastly, most of the cognitive tests were administered during a hemodialysis session. Recently, Murray *et al.* showed that global cognitive function varies significantly over the course of the dialysis session; performance is worst during the session itself and best shortly before the session or on the day after.¹⁸ In patients undergoing peritoneal dialysis, the few available data suggest that the prevalence of cognitive impairment might be lower than in hemodialysis patients.^{19,20} However, this apparent discrepancy may reflect selection bias (because the dialysis procedure will depend on the patients' characteristics and thus cognitive function before the introduction of dialysis²¹) rather than the procedure's characteristics *per se*.

Patients with Mild to Moderate CKD

Cognitive impairment in CKD is not limited to patients with stage 5 CKD. Several cross-sectional studies have suggested its occurrence in earlier stages of kidney disease (Table 2). Thus, estimated GFR (eGFR) was inversely related to global performance in global cognitive function tests.^{6,22,23} Yaffe *et al.* confirmed this observation by applying a more detailed battery of neuropsychological tests.²⁴ They reported that an inverse relation between eGFR and global cognitive function was observed for most cognitive domains, but the pattern of cognitive impairment differed from one CKD subgroup to another. Patients with advanced CKD (defined as eGFR < 30 ml/min per 1.73 m²) were more likely to have cognitive impairment as revealed by tests evaluating global cognition, naming, attention, executive function, and delayed memory, but not tests assessing fluency and immediate memory, compared with patients with mild or moderate CKD (defined as an eGFR 45–59 ml/min per 1.73 m²).

The results of longitudinal studies also suggest that CKD is an independent risk factor for cognitive impairment because

lower eGFR at study enrollment is associated with a more rapid rate of cognitive decline.^{25–28} In the Cardiovascular Health Cognition Study, the first study devoted to this topic, Seliger *et al.* reported that after adjustment for potential confounders, moderate kidney failure is associated with a 37% increase in the risk for dementia.²⁸ In a population of 3034 community-dwelling older adults, Kurella *et al.* also showed that CKD, defined as an eGFR < 60 ml/min per 1.73 m², is associated with an increased risk for cognitive impairment. Furthermore, the risk for cognitive impairment in this population varied according to the severity of CKD, suggesting a causal relation.²⁷ This association has been confirmed by other recent studies.^{25,26}

However, two other studies failed to show an association between CKD at baseline and the risk for cognitive decline.^{29,30} In the first, a prospective, cohort study of 5529 healthy older men, Slinin *et al.* found an independent association between mild to moderate reductions in kidney function and executive function at baseline but not at the end of the follow-up period.³⁰ Recently, data from the 3C population-based cohort study, which included 7839 patients older than age 65 with 7 years of follow-up and baseline eGFR < 60 ml/min per 1.73 m², were not associated with an increased risk for incident dementia or cognitive decline.²⁹ However, in this latter study, the percentage of participants with CKD was relatively low (12% with a baseline eGFR < 60 ml/min per 1.73 m²). Furthermore, the patients had a relatively low cardiovascular risk profile, in line with the low prevalence of CKD. This precludes generalization of the study findings to patient populations with more advanced CKD.

BRAIN IMAGING IN CKD PATIENTS

Clinically Evident Stroke and Subclinical Cerebrovascular Disease in CKD Patients

Patients with CKD display a high prevalence of stroke. According to the U.S.

Renal Data System, the prevalence is 17% for patients undergoing long-term hemodialysis, 10% for patients with mild to moderate CKD, and 4% in the non-CKD population, after accounting for age, sex, and race.² A history of stroke doubles the risk for dementia in both CKD and non-CKD populations.² Furthermore, CKD patients have an increased prevalence of subclinical cerebrovascular disease, with silent brain infarcts (SBIs), cerebral infarcts detected by brain imaging in the absence of clinical symptoms, more white matter lesions (WMLs), and more microbleeds (Figure 1).³¹

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

Study	Design	Population	Cognitive Tests	Renal Function Assessment	Results	Limitations
Kurella <i>et al.</i> , 2004 ⁶	Cross-sectional study	80 hemodialysis patients and 80 CKD patients ≥20 yr Mean age, 63 yr	3 tests: 3MS, TMT B, and CVLT Cognitive impairment if: 3MS score < 80 TMT B=300 s CVLT: recall of < 4 words or more than 2 SDs from mean CVLT score	MDRD (6 items)	Graded relation between cognitive function and severity of CKD In hemodialysis patients: see Table 1 In CKD patients: 3MS score < 80 in 15% of patients TMT B=300 s in 23% of patients CVLT: abnormal score in 28% of patients	No control group (results compared with published norms) No established cutoffs for CVLT
Seliger <i>et al.</i> , 2004 ²⁸ (CHCS)	Cohort study	Population of community-dwelling older adults free of dementia at baseline 3349 patients ≥ 65 yr Median follow-up, 6 yr Mean age, 75 yr	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 " SCR ≥ 1.5 mg/dl for men	477 incident dementia cases during follow-up: Vascular-type dementia: n=211 Alzheimer-type dementia: n=244 Moderate renal impairment associated with 37% increased risk for dementia (95% CI, 1.06–1.78)	Cases of incident dementia were identified retrospectively Renal function at baseline assessed by reciprocal of SCR (1/SCR)
Kurella <i>et al.</i> , 2005 ⁸⁴ (HERS)	Cross-sectional study	1015 women < 80 yr with established coronary artery disease Mean age, 67 yr	3MS (cognitive impairment if 3MS score < 80) TMT B Modified Boston naming test Verbal fluency test Word list memory test Word list recall test	MDRD (6 items)	Risk for global cognitive impairment was increased 5-fold in women with eGFR < 30 ml/min per 1.73 m ² 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 ² decrement in eGFR)	Selected population Hemoglobin and hematocrit values not collected
Kurella <i>et al.</i> , 2005 ²³ (HABCS)	Longitudinal study	3034 community-dwelling older adults Mean age, 74 yr	3MS (at baseline and at 2 and 4 yr of follow-up) Cognitive impairment defined as 3MS score < 80 or decline in 3MS >5 points after 2 or 4 yr of follow-up among participants with baseline 3MS scores >80	MDRD (4 items) CKD defined as eGFR < 60 ml/min per 1.73 m ²	Lower baseline eGFR is associated with cognitive impairment CKD is associated with increased risk (86%) for cognitive impairment: OR, 1.32 (eGFR 45–59 ml/min per 1.73 m ²) OR, 2.43 (eGFR <45 ml/min per 1.73 m ²) 0.8% of patients had moderate CKD Moderate CKD associated with: Poorer learning/concentration (OR, 2.41) Impairment in visual attention (OR, 2.74)	Only 1 measurement of serum creatinine (at baseline)
Hailem <i>et al.</i> , 2007 ²² (NHANES III)	Cross-sectional study	4849 young healthy adults (age 20–59 yr) Mean age, 36 yr	Visual motor reaction time Visual attention Learning/concentration	MDRD (4 items) Moderate CKD defined as eGFR 30–49 ml/min per 1.73 m ²		Small number of CKD patients Limited cognitive assessment MDRD equation not validated in nonwhite populations

Table 2. Continued

Study	Design	Population	Cognitive Tests	Renal Function Assessment	Results	Limitations
Kurella Tamura et al., 2008 ²⁷ (REGARDS)	Cross-sectional study	23405 patients \geq 45 yr Mean age, 65 yr	6-item cognitive screening examination Cognitive impairment defined as score \leq 4	MDRD (4 items) CKD defined as eGFR < 60 ml/min per 1.73m ²	11% of patients had CKD and 8% had cognitive impairment CKD was associated with increased prevalence of cognitive impairment (OR, 1.23)	Insensitive measurement of cognitive function Cognitive assessment by telephone interview
Slinin et al., 2008 ³⁰ (MROS)	Observational prospective cohort study	5529 community-dwelling men \geq 65 yr Mean follow-up, 5 yr Mean age, 74 yr	3MS (cognitive impairment defined as 3MS < 80) TMT B (cognitive impairment defined as TMT B time > 1.5 SDs above the mean)	MDRD (4 items) 3 eGFR groups (ml/min per 1.73 m ²): eGFR > 60 45 < eGFR < 60 eGFR < 45	-3MS score < 80 in 15% of patients, TMT B = 300 s in 23% of patients Association between worse renal function and higher odds of impairment based on TMT B test score at baseline No association between eGFR and cognitive decline during the follow-up	Limited neuropsychological tests Healthy participant population
Egten et al., 2009 ²⁶ (INVADE)	Cohort study	3679 community-dwelling adults 2-yr follow-up Mean age, 68 yr	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 > 7	Cockcroft-Gault equation for eGFR (ml/min per 1.73m ²): \geq 60: normal 45-59: mild <45: moderate	At baseline, 11% had cognitive impairment After 2-yr follow-up: 6.2% patients with new cognitive impairment: No CKD: 5.8% Mild CKD: 9.9% Moderate CKD: 21.5% 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)	No association between CKD and cognitive impairment with use of MDRD equation Short follow-up Limited cognitive assessment
Yaffe et al., 2010 ²⁴ (CRICS)	Cross-sectional study	825 CKD patients Age \geq 55 yr	Global cognition Naming Attention Executive functions Memory delayed Category fluency	MDRD (4 items) Advanced CKD: eGFR 45-59 ml/min per 1.73 m ² Mild to moderate CKD: eGFR < 30 ml/min per 1.73 m ²	Participants with lower eGFR had lower cognitive scores on most cognitive domains Participants with advanced CKD were more likely to have clinically significant cognitive impairment on most cognitive domains than those with mild to moderate CKD	MDRD equation not validated in nonwhite populations (45% of patients were black) Small sample of patients without CKD (n=80)
Buchman et al., 2009 ²⁵ (RMAP)	Observational cohort study	886 community-dwelling elderly adults without dementia, followed up for 3.4 yr Mean age, 81 years	Neuropsychological tests performed at baseline and annually: MMSE 19 tests for 5 domains (semantic memory, episodic memory, working memory, visuospatial abilities, and perceptual speed)	MDRD (4 items) CKD defined as eGFR < 60 ml/min per 1.73 m ²	CKD at baseline was associated with faster rate of cognitive decline CKD associated with altered semantic memory, episodic memory, and working memory but not visuospatial abilities or perceptual speed	No measure of inflammatory markers Selected (older) patients

3MS, Modified Mini-Mental Test 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 creatinine; 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.

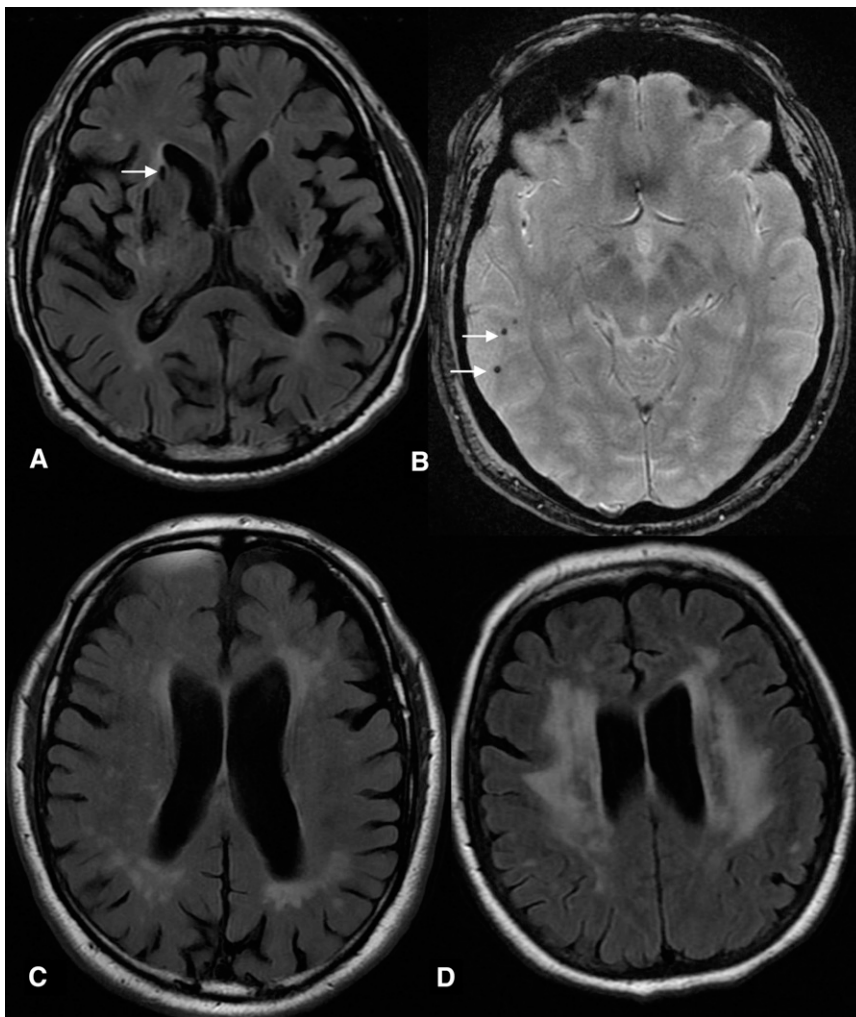


Figure 1. Subclinical brain lesions in CKD patients. (A) Axial fluid-attenuated inversion recovery magnetic resonance image showing silent brain lacunar infarct (arrow). (B) Axial gradient-echo magnetic resonance imaging sequence showing multiple microbleeds (small foci of hypointensity, arrows) located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

with CKD, independently of other established risk factors.⁴⁰

Likewise, the prevalence of WMLs is high (up to 70%) in both CKD patients and stroke patients.^{9,41,42} This is not surprising, given that WMLs are thought to be symptomatic of a progressive, irreversible process that follows on from arteriosclerosis.⁴³ Most cross-sectional, population-based studies show a strong association between eGFR on one hand and white matter volume and WMLs on the other.^{44–46} Only Martinez-Vea *et al.* failed to report a statistically significant relationship between vascular nephropathy and WMLs in a multivariate

analysis.⁴⁷ 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.⁴⁸ 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 hemodialysis⁴⁹ and also in patients with a more moderate decrease in renal function.⁵⁰ In two other studies performed in patients with ischemic stroke, similar associations between chemical markers

of CKD and cerebral microbleeds have been observed.^{51,52} 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*.⁵³ 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.⁵⁴

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.⁵⁵ Hence, impaired cerebral hemodynamics, as evaluated by transcranial Doppler ultrasonography, may reveal interesting information on the association between altered cerebrovascular hemodynamics and cognitive impairment.⁵⁶ 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.^{57,58} Additionally, the prevalence of traditional

Table 3. Main brain imaging studies in CKD patients

Study	Design	Population	Renal Function Assessment	Imaging	Results	Limitations
Fazekas et al., 1995 ⁹	Cross-sectional study	60 hemodialysis patients age \geq 35 yr Mean age, 58 yr	On dialysis	MRI 1.5 T	CKD associated with: Cortical atrophy (50%) White matter hyperintensities (80%) Ischemic abnormalities (63%)	Small sample size
Seliger et al., 2005 ⁸⁵	Cross-sectional study	2784 elderly (\geq 65 yr)	Serum creatinine and cystatin-C	MRI 1.5 T SBI defined as infarct-like lesion \geq 3 mm in participant without previous stroke or TIA	SBI were present in 789 patients (28%) Prevalence of SBIs was directly associated with quintile of cystatin-C, whereas association between SCR and SBI was U-shaped Microbleeds were present in 11 of 57 patients (19%)	Cross-sectional design CHS participants who completed cranial MRI were healthier than those who did not
Yokoyama et al., 2005 ⁴⁹	Cross-sectional study	57 patients on hemodialysis	On dialysis	MRI 0.5 T Microbleeds defined as homogeneous rounded lesions with diameter of 2–5 mm on T2*-weighted gradient echo imaging		Small sample size
Ikram et al., 2008 ⁴⁴ (RSS)	Cross-sectional study	484 participants age \geq 60 yr Mean age, 73 yr	Cockcroft-Gault equation	MRI 1.5 T with: Automated MRI analysis of lobar and deep volumes of gray matter and white matter, and volume of whitematter lesions Lacunar infarcts were rated visually	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	Only 1 measurement of eGFR No distinction between lacunar infarcts and dilated perivascular spaces
Kobayashi et al., 2009 ⁸⁶	Cross-sectional study	375 patients (335 CKD patients and 40 hypertensive patients) Mean age, 63 yr	MDRD formula CKD defined as eGFR $<$ 60 ml/min per 1.73 m ²	MRI 1.5 T SBI defined as focal area \geq 3 mm and $<$ 20 mm in diameter in both T1- and T2-weighted sequences	There was graded association between eGFR (ml/min per 1.73 m ²) 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 \leq 15: OR, 2.51 (95% CI, 1.91–3.10) (versus eGFR \geq 60 ml/min per 1.73 m ²)	No healthy control group
Khatri et al., 2007 ⁴⁵ (NOMAS)	Cross-sectional	615 community-based patients age \geq 55 yr Mean age, 70 yr	MDRD formula, Cockcroft-Gault equation	MRI 1.5 T Quantitative analysis of white matter hyperintensities (log-white matter hyperintensity volume)	Association between moderate to severe CKD (eGFR 15–59 ml/min/1.73 m ²) and white matter hyperintensities	MRI sample healthier than overall cohort
Cho et al., 2009 ⁵¹	Cross-sectional	152 ischemic stroke patients	MDRD equation (4 items)	MRI 1.5 T Assessment of cerebral microbleeds using gradient echo MRI	Hypertension, white matter lesions, old age, and low GFR (OR, 3.85) were associated with cerebral microbleeds	Small number of patients Population limited to ischemic stroke patients
Bugnicrot et al., 2009 ³⁶	Cross-sectional	Patients with neurologic disorders	MDRD formula	Multidetector CT	Association between intracranial artery calcification and eGFR	Study limited to population with neurologic disorders
Kobayashi et al., 2010 ⁴⁰	Prospective cohort study	142 CKD patients (stages 3–5) followed up for 2 yr	MDRD formula	MRI 1.5 T SBI defined as focal area \geq 3 mm and $<$ 20 mm in diameter in both T1- and T2-weighted sequences Primary outcome was doubling of serum creatinine level, development of ESRD (defined as dialysis or transplant) and death from cardiovascular causes	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	Small sample size Hospital-based cohort

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.

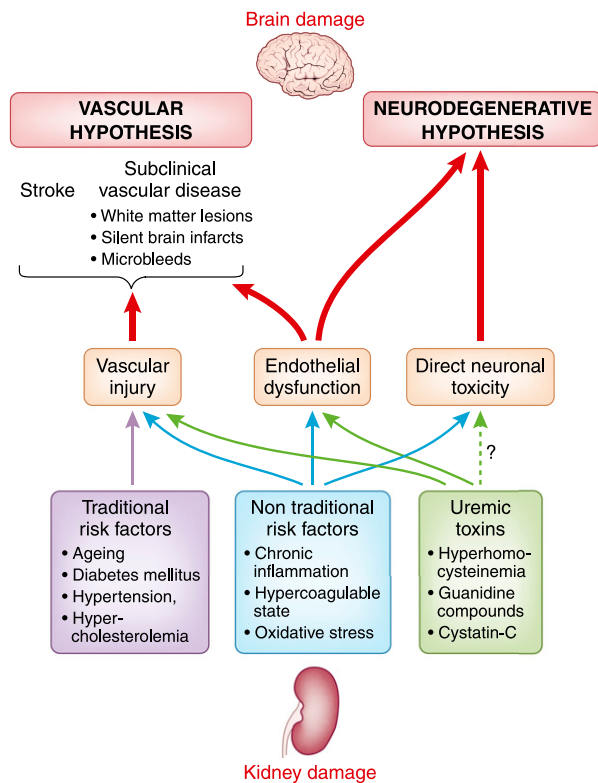


Figure 2. Schematic representation of potential causes of cognitive impairment in patients with CKD.

vascular risk factors, such as arterial hypertension, 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 pathogenesis of cognitive impairment in CKD patients.

Furthermore, it has been suggested that vascular disease is a more likely cause of cognitive impairment than is Alzheimer'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 vascular component.²⁹ 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 psychomotor speed resembles the situation in stroke.⁵⁹ However, the results of a neuropathologic study indicates that

patients with small-vessel cerebrovascular disease present broader cognitive impairment, which can also include memory deficits. These findings thus challenge the utility of executive impairment as a diagnostic marker for vascular cognitive impairment or dementia.⁶⁰

Nontraditional vascular risk factors, such as hyperhomocysteinemia, hypercoagulable states, inflammation, and oxidative stress, have also been linked to cognitive impairment.⁶¹ These factors could accelerate the progression of atherosclerosis and vascular endothelial dysfunction, both of which are associated with dementia risk.^{62,63} Interestingly, elevated homocysteine levels are present in 85% of dialysis patients but only 10% of the general population.⁶⁴ In a prospective cohort study, plasma homocysteine 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 homocysteine 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 homocysteine has a direct, neurotoxic effect by activating the N-methyl-D-aspartate receptor or by conversion into homocysteic acid, leading to cell death.⁶⁹ Furthermore, clinical studies show that elevated plasma homocysteine concentrations are associated with an increased risk for Alzheimer disease.⁷⁰ However, lowering homocysteine 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 abnormalities mentioned above can only partly explain the high frequency of vasculopathy-related cognitive disorders observed in CKD patients. Hence, other disease mechanisms are necessarily involved. First, chronic hypertension and numerous vascular risk factors are associated with an increased risk for Alzheimer disease.⁷² Conversely, the results of observational studies and clinical trials suggest that antihypertensive drugs may decrease age-related cognitive decline and dementia, 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 dementia.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 neurodegenerative dementia.^{75,76} During the past decade, most studies have focused on the observation that beneficial effects of various antihypertensive drugs in preventing 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

they prevent angiotensin-converting enzyme-mediated conversion of $A\beta_{42}$ into $A\beta_{40}$, 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.⁷⁸ Various uremic toxins have been implicated in the pathogenesis of cognitive impairment.⁷⁹ 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.⁸⁰ 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.⁸⁰ It is well known that these uremic guanidine compounds are neuroexcitatory agents and have convulsant activity in animal studies.⁸¹ 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.⁸² 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.⁸³ 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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