Frequency of and risk factors for poor cognitive performance in hemodialysis patients

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ABSTRACT

Objective: There are few detailed data on cognition in patients undergoing dialysis. We evaluated the frequency of and risk factors for poor cognitive performance using detailed neurocognitive testing.

Methods: In this cross-sectional cohort study, 314 hemodialysis patients from 6 Boston-area hemodialysis units underwent detailed cognitive assessment. The neuropsychological battery assessed a broad range of functions, with established age-, sex-, and education-matched normative scores. Principal component analysis was used to derive composite scores for memory and executive function domains. Risk factors for each domain were evaluated using linear regression adjusting for age, sex, race, and education status. Analyses were repeated in those with Mini-Mental State Examination (MMSE) score ≥24.

Results: Compared with population norms, patients on dialysis had significantly poorer executive function but not memory performance, a finding that persisted in the subgroup with MMSE score ≥24. In adjusted analyses, vascular risk factors and vascular disease were associated with lower executive function ($p < 0.01$).

Conclusions: There is a high frequency of poor cognitive performance in hemodialysis patients, primarily affecting executive function. Risk factors for worse executive function include vascular risk factors as well as vascular disease. Normal performance on the MMSE does not preclude impaired cognitive function, because individuals with MMSE score ≥24 also have a high frequency of poor cognitive performance. *Neurology*® 2013;80:471–480

GLOSSARY

CESD = Center for Epidemiological Studies Depression Scale; **COWAT** = Controlled Oral Word Association Test; **DCI** = Dialysis Clinic Inc.; **ESRD** = end-stage renal disease; **MMSE** = Mini-Mental State Examination; **PCA** = principal component analysis; **WBC** = white blood cell.

Cognitive impairment in dialysis is an increasingly important public health problem given the aging end-stage renal disease (ESRD) population and the increasing prevalence of diabetes and vascular disease. In older studies in hemodialysis patients, cognitive impairment, defined by poor performance on the Mini-Mental State Examination (MMSE), was present in 40% to 60%.[1–3] Despite the fact that the MMSE remains the most frequently used screening tool for cognitive impairment, it focuses on memory and largely neglects other cognitive domains such as executive function; accordingly, the MMSE may not be sufficient to detect more subtle degrees of cognitive impairment.

The major causes of dementia in the general population are Alzheimer disease, which initially manifests with memory loss with later involvement of other cognitive domains, and vascular dementia, which primarily manifests with impairment in executive function.[4–7] Although it is likely that patients undergoing dialysis have similar causes for cognitive impairment as the general population, there are few studies that have attempted to distinguish the prevalence of and risk factors for each type of cognitive impairment in this population.

The goals of this study were therefore to evaluate the frequency of and risk factors for poor cognitive performance in hemodialysis patients using detailed measures of multiple cognitive domains,

Supplemental data at www.neurology.org

Supplemental Data

From the Division of Nephrology (M.J.S., K.V.L., E.P.S., L.M.G., D.A.D., K.S., D.E.W.), Department of Medicine, Department of Psychiatry (T.M.S.), and Biostatistics Research Center (H.T.), Tufts Medical Center, Boston; Division of Nephrology (J.A.S.), St. Elizabeth's Medical Center, Brighton; and Division of Nephrology (A.K.S.), Brigham and Women's Hospital, Boston, MA.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The results presented in this article have not been published previously in whole or part, except in abstract format. An abstract based on the content of this manuscript was accepted as a poster at the American Society of Nephrology Annual Meeting in Philadelphia in 2011.

to compare these data with general population norms, and, in patients with MMSE score ≥24, to assess the proportion with cognitive impairment using more detailed testing.

METHODS Outpatients older than 18 years receiving chronic in-center hemodialysis at 5 Dialysis Clinic Inc. (DCI) units and 1 hospital-based unit (St. Elizabeth's Medical Center) in the greater Boston area were screened for the Cognition and Dialysis Study. Reflecting the nature of the cognitive battery, eligibility criteria included English fluency as well as sufficient visual and hearing acuity to complete cognitive testing. To minimize cognitive testing floor effects and reflecting inability to provide consent, individuals with MMSE score ≤10 and/or advanced dementia based on medical record review were excluded. Nonaccess-related hospitalization within 1 month, receipt of hemodialysis for <1 month, and single-pool Kt/V (a measure of dialysis dose) <1.0 were temporary exclusion criteria.

Standard protocol approvals, registrations, and patient consents. The Tufts Medical Center/Tufts University Institutional Review Board approved the study and all participants who completed the detailed cognitive testing signed informed consent.

Neuropsychological assessment. Participants were administered a battery of cognitive tests by research assistants after training and direct observation by the study neuropsychologist (Dr. Scott). To maintain quality and interrater reliability, testing was observed by the study neuropsychologist at 3- to 6-month intervals. To limit subject fatigue, all testing was completed during the first hour of hemodialysis. When possible, we also performed neurocognitive testing in a private room or in as quiet an environment as possible. The neuropsychological battery included well-validated frequently used cognitive tests that possess high inter- and intrarater reliability and have established age-, sex-, and/or education-matched normative scores. The MMSE[8] was used as a screening test, and the North American Adult Reading Test served as a measure of premorbid verbal IQ.[9] The neurocognitive battery consisted of the Wechsler Memory Scale-III Word List Learning Subtest,[10] the Wechsler Adult Intelligence Scale-III Block Design[10] and Digit Symbol-Coding Subtests,[10] and Trail Making Tests A and B[11] (Trails A and B) (table e-1 on the *Neurology®* Web site at www.neurology.org). During the last 2 years of the study, the cognitive panel was expanded to include additional verbal tests assessing both memory and executive functions, including Digit Span (forwards and backwards),[10] the Mental Alternation Test,[12] and the Controlled Oral Word Association Test (COWAT).[13] The overall battery assesses a broad range of functioning including global ability, supraspan learning, auditory retention, visual retention, attention/mental processing speed, visual construction/fluid reasoning, and motor speed. We also evaluated depression using the Center for Epidemiological Studies Depression Scale (CESD).[14]

Factors associated with cognitive impairment. Demographic, clinical, and laboratory factors were ascertained at the time of cognitive testing. Demographic data (age, sex, and race) were obtained via participant report, medical charts, and the DCI and St. Elizabeth's Medical Center databases. Education (<12th grade, high school graduate, and ≥2 years of college) was obtained via patient questionnaire. Medical history, including myocardial infarction and coronary revascularization (which were used to define coronary disease), peripheral vascular disease, stroke, heart failure, presence of diabetes, hypertension, and smoking, were defined by patient history or documentation in the patient's electronic or paper chart. Additionally, DCI electronic medical records and paper records were reviewed for a history of these conditions with specific focus on problem lists, hospital discharge summaries, cardiac testing results, and procedure results. Cause of ESRD and dialysis vintage were obtained from the DCI or St. Elizabeth's electronic record as were physical examination findings of mean monthly systolic and diastolic blood pressures and body mass index. Predialysis blood tests included albumin, hematocrit, phosphorus, intact parathyroid hormone, white blood cell (WBC) count, C-reactive protein, and single-pool Kt/V. All DCI laboratory tests were measured in a central laboratory in Nashville, TN.

Statistical analysis. Continuous variables were presented as mean (SD) or median (interquartile range) as appropriate and categorical variables as proportions. The study population was compared with eligible but nonrecruited dialysis patients using χ^2 tests for categorical data and *t* tests and the nonparametric Wilcoxon test for continuous data. Test scores in participants with and without history of stroke were standardized for age, sex, and education where appropriate before comparison with population-based normative data. The percentage of dialysis patients with test scores >1, >1.5, and >2 SDs below expected population norms was reported. A 1-sample *t* test was used to evaluate differences between dialysis patients and normative data. For the Mental Alternation Test and the COWAT, normal values were extrapolated from published data, with impairment defined as a score <15 on the Mental Alternation Test[15–17] and below the age- and education-adjusted 25th percentile fluency scores for the COWAT.[15,18]

Principal component analysis (PCA) with varimax rotation was used as a data-reduction technique to derive composite scores for separate cognitive domains in the entire study population.[19] Two principal components with eigenvalues >2 were obtained, and the resulting component scores were subsequently used as a dependent variable in linear regression analyses. The first component was primarily comprised of Word List Learning Recall and Recognition and was interpreted to reflect memory (table e-1). The second component was interpreted to reflect executive functioning, attention, and processing speed (referred to as executive function within the Results section), with Trails A and B, Block Design, and Digit Symbol-Coding tests contributing substantially. Digit Span, Mental Alternation Test, and the COWAT were not used in calculation of the PCA because of the smaller number of individuals who completed these tests. There were 274 individuals with complete testing on Trails A and B, Blocks, Digit Symbol, and components of the Word List Learning Subtest. For 18 individuals who were missing results on 1 cognitive test (or 2 results if derived from the same test), single-item imputation was performed using multivariable linear regression models based on performance on other tests in the cognitive battery. These imputations results were incorporated to derive the PCA but were not used for evaluating performance on individual cognitive tests. The total number for the PCA analysis was therefore 292. The relationship between risk factors and cognitive domains was assessed in multivariable linear regression models adjusted for age, sex, race, and education. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC). Differences were considered statistically significant at *p* values <0.05.

Sensitivity analyses. Analyses were repeated excluding patients with a history of stroke and excluding patients with MMSE score <24. Because some cognitive testing may be dependent on manual dexterity that is hindered during hemodialysis because of arteriovenous access in the dominant arm, we performed a sensitivity analysis limiting the study population to those individuals who performed testing using their dominant hand in an unencumbered manner. In additional analyses, we adjusted for depression (CESD) because it may have an effect on cognitive function. Furthermore, we evaluated the shape of the relationship of dialysis vintage with cognitive function and adjusted for nonlinear effects in multivariable analyses.

RESULTS **Baseline information.** Among 929 patients screened, 414 were ineligible for complete cognitive

testing (figure). Of the remaining 515 individuals, 314 underwent more detailed cognitive testing. Patients who were eligible but did not enroll were slightly older (aged 66 vs 63 years, $p = 0.05$) and had slightly lower serum albumin (3.7 vs 3.8 g/dL, $p = 0.01$), but otherwise had similar demographic and clinical characteristics. The mean age of study participants was 63 years; 22% were African American, 46% were women, and 90% had a high school or higher education level (table 1).

Comparisons with normative data. Mean (SD) MMSE score was 26.7 (2.8), with 42 participants (13.4%) scoring <24. Of these, 17 had MMSE scores ≤21 and 6 had MMSE scores ≤18. Because an additional 36 dialysis patients were excluded based on advanced dementia, a total of 22% (36 + 42 of 350) of potentially eligible hemodialysis patients therefore had cognitive impairment defined by MMSE score <24.

When considering cognitive tests that associate primarily with memory processes, it was noted that performance on delayed recall was slightly higher in hemodialysis patients in comparison with general population norms (table 2), whereas performance on immediate recall and recognition was significantly lower in hemodialysis patients. When considering cognitive tests that associate primarily with executive processes, results on all tests were significantly lower in hemodialysis patients compared with general population norms, with as many as 30% to 40% of

Figure Flow diagram of enrolled patients

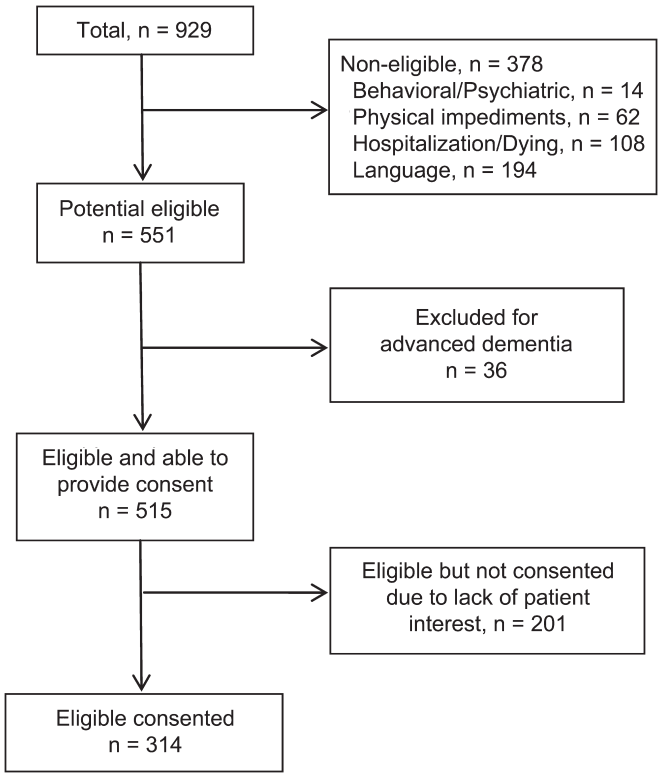

Table 1 Baseline characteristics of the study sample[a]

	Total (N = 314)
Age, y	63 (16)
Female, %	46.5
African American, %	22.3
Education level, %	
<12th grade	9.9
High school graduate	54.8
≥2 y college	35.4
Coronary artery disease, %	36.9
Peripheral vascular disease, %	23.6
History of CVD[b]	43.9
Stroke, %	17.8
Heart failure, %	36.0
Diabetes, %	47.8
Hypertension, %	89.2
Smoking status, %	
Never	38.4
Past	52.8
Current	8.9
Primary cause of ESRD, %	
Diabetes	34.7
Glomerulonephritis	17.8
Hypertension	18.8
Other	16.2
Unknown	12.4
Dialysis vintage, mo	14 (7–35)
<12 mo, %	40.5
12 to <24 mo, %	25.1
24 to <36 mo, %	9.9
≥36 mo, %	24.5
Systolic blood pressure, mm Hg	141 ± 21
Diastolic blood pressure, mm Hg	73 ± 12
Body mass index, kg/m^2	28 ± 7
Albumin, g/dL	3.8 ± 0.4
Hematocrit, %	36 ± 4
Phosphate, mg/dL	5.5 ± 1.5
Intact PTH, pg/mL	228 (146–396)
White blood cell count, ×10^3/μL	7.4 ± 2.3
CRP, mg/L	5.3 (2.2–11.5)
spKt/V	1.51 ± 0.24

Abbreviations: CRP = C-reactive protein; CVD = cardiovascular disease; ESRD = end-stage renal disease; PTH = parathyroid hormone; spKt/V = single-pool Kt/V (a measure of dialysis dose).
[a] Data are presented as percentage, mean (SD), or median (25th–75th percentile).
[b] History of CVD is defined as the presence of peripheral vascular disease or coronary artery disease.

Table 2 Cognitive function in hemodialysis patients compared with normative data[a]

		Dialysis patients					Comparisons (proportion below reference),[b] proportion (95% CI)		
Test	Test description	No.	Raw values, mean (SD)	Rescaled, mean (SD)	Normative data, reference (SD)	One-sample *t* test, *p* value	1 SD	1.5 SD	2 SD
MMSE score	Screen	314	26.7 (2.8)	26.7 (2.8)	"Normal" ≥24	NA	13.4 (9.8, 17.7)[c]		
NAART VIQ	Intelligence	311	102.3 (12.2)	102.3 (12.2)	100 (15)	0.001	8.4 (5.5, 12.0)	1.6 (0.5, 3.7)	0.0
Delay recall	Primarily memory, learning, and recognition[d]	309	4.4 (2.7)	10.5 (2.6)	10 (3)	<0.001	6.5 (4.0, 9.8)	1.3 (0.4, 3.3)	0.0
Immediate recall		312	23.8 (7.2)	7.5 (3.2)	10 (3)	<0.001	41.4 (35.8, 47.0)	29.2 (24.2, 34.6)	8.3 (5.5, 12.0)
Recognition		310	20.7 (3.0)	9.2 (3.1)	10 (3)	<0.001	18.4 (14.2, 23.2)	11.9 (8.5, 16.1)	5.5 (3.2, 8.6)
Block Design	Primarily executive functioning, attention, and processing speed[e]	307	26.1 (10.6)	8.7 (2.8)	10 (3)	<0.001	22.2 (17.6, 27.2)	12.4 (8.9, 16.6)	0.7 (0.1, 2.3)
Digit Symbol		282	40.1 (17.0)	6.8 (2.6)	10 (3)	<0.001	51.8 (45.8, 57.7)	34.4 (28.9, 40.3)	7.1 (4.4, 10.7)
Digit Span		165	15.2 (3.9)	9.6 (2.8)	10 (3)	0.06	12.1 (7.6, 18.1)	3.6 (1.4, 7.8)	0.6 (0.0, 3.3)
Trail A		293	61.3 (39.6)	38.2 (9.6)	50 (10)	<0.001	54.6 (48.7, 60.4)	38.2 (32.6, 44.1)	17.8 (13.6, 22.6)
Trail B		289	136.9 (64.7), 20.8% noncompletion	37.1 (11.3)	50 (10)	<0.001	59.5 (53.6, 65.2)	39.5 (33.8, 45.3)	26.0 (21.0, 31.4)
COWAT total		167	35.9 (11.1)	40.0 (10.3)	"Impaired" ≤40.7 (lowest quartile of general population)	NA		53.9 (46.0, 61.6)[c]	
Mental Alternation		167	20.0 (7.6)	Same as raw score	"Impaired" <15 alternations[f]	NA		25.8 (19.3, 33.1)[c]	
CESD	Depression	311	10.6 (8.1)	Same as raw score	Depression likely present with CESD score >16	NA		21.9 (17.4, 26.9)[c]	

Abbreviations: CESD = Center for Epidemiological Studies Depression Scale; CI = confidence interval; COWAT = Controlled Oral Word Association Test; MMSE = Mini-Mental State Examination; NA = not available; NAART VIQ = North American Adult Reading Test verbal IQ; Trail A = Trail Making Test A; Trail B = Trail Making Test B.

[a] Test results are mean ±SD. Raw scores represent number correct, except for Trails A and B, which are reported in seconds required to complete the task. All rescaled scores except Trails A and B are standardized for age and reported as scaled scores centered at 10. Trails A and B report *t* scores standardized for age, sex, and education and are centered at 50. Higher scores are consistent with better performance on all tests.

[b] The proportions in the <1 SD column refer to all people with SD <1, therefore including those with SD <1.5 and <2. Similarly, the <1.5 SD column includes those with SD <1.5 and <2 whereas the SD <2 column refers to only those with SD <2; accordingly the values in these 3 columns cannot be added to obtain the percentage with abnormalities.

[c] For tests without established population norms and SDs, the percentage with scores consistent with poor performance is listed.

[d] Primarily memory, learning, and recognition refers to rows "Delay Recall" through "Recognition."

[e] Primarily executive functioning, attention, and processing speed refers to rows "Block Design" through "Mental Alternation."

[f] Defined in an HIV population with the MMSE score <24 as the gold standard.[17] When the proportion was 0% or 100%, the 95% CI was not calculated.

Table 3 Relationship of risk factors to the principal component analysis memory score[a]

	All				No stroke			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	β (95 CI)	*p* Value	β (95 CI)	*p* Value	β (95 CI)	*p* Value	β (95 CI)	*p* Value
Age, y	−0.34 (−0.44, −0.24)	<0.0001	−0.37 (−0.47, −0.27)	<0.0001	−0.35 (−0.46, −0.24)	<0.0001	−0.37 (−0.48, −0.26)	<0.0001
Female	0.42 (0.20, 0.63)	0.0001	0.42 (0.23, 0.62)	<0.0001	0.45 (0.21, 0.69)	0.0003	0.46 (0.23, 0.68)	<0.0001
African American	0.07 (−0.19, 0.33)	0.59	−0.28 (−0.53, −0.03)	0.03	0.12 (−0.18, 0.41)	0.44	−0.22 (−0.51, 0.06)	0.12
Education, ref. <12th grade								
≥2 y of college	0.24 (−0.15, 0.63)	0.22	0.17 (−0.19, 0.52)	0.35	0.22 (−0.23, 0.66)	0.34	0.11 (−0.29, 0.52)	0.57
High school graduate	−0.05 (−0.42, 0.33)	0.81	−0.13 (−0.46, 0.21)	0.45	−0.04 (−0.46, 0.39)	0.86	−0.13 (−0.51, 0.26)	0.51
Coronary artery disease	−0.21 (−0.43, 0.01)	0.07	0.15 (−0.07, 0.37)	0.18	−0.19 (−0.45, 0.07)	0.16	0.24 (−0.02, 0.50)	0.07
Peripheral vascular disease	−0.18 (−0.43, 0.08)	0.18	0.09 (−0.15, 0.34)	0.44	−0.18 (−0.48, 0.12)	0.23	0.14 (−0.14, 0.43)	0.32
History of CVD[b]	−0.27 (−0.49, −0.05)	0.01	0.10 (−0.12, 0.32)	0.35	−0.26 (−0.51, −0.01)	0.04	0.18 (−0.08, 0.43)	0.17
Stroke	−0.29 (−0.58, −0.01)	0.05	−0.17 (−0.43, 0.09)	0.21				
Heart failure	−0.26 (−0.48, −0.03)	0.03	−0.04 (−0.26, 0.17)	0.68	−0.29 (−0.55, −0.03)	0.03	−0.04 (−0.29, 0.20)	0.73
Diabetes	−0.08 (−0.30, 0.14)	0.49	0.08 (−0.12, 0.28)	0.43	−0.03 (−0.28, 0.22)	0.81	0.13 (−0.11, 0.36)	0.29
Hypertension	−0.02 (−0.39, 0.34)	0.90	0.11 (−0.22, 0.44)	0.50	−0.08 (−0.50, 0.35)	0.72	0.09 (−0.30, 0.47)	0.66
Smoking status, ref., prior								
Smokes currently	0.13 (−0.26, 0.52)	0.52	0.00 (−0.37, 0.36)	0.99	0.04 (−0.42, 0.50)	0.86	−0.14 (−0.57, 0.30)	0.54
Never smoked	0.22 (−0.02, 0.45)	0.07	−0.03 (−0.26, 0.20)	0.79	0.21 (−0.06, 0.48)	0.12	−0.04 (−0.30, 0.21)	0.73
Primary cause of ESRD, ref. GN								
Diabetes	−0.17 (−0.49, 0.15)	0.30	0.15 (−0.15, 0.45)	0.33	−0.13 (−0.48, 0.23)	0.49	0.17 (−0.16, 0.51)	0.31
Hypertension	−0.41 (−0.77, −0.05)	0.03	−0.03 (−0.37, 0.31)	0.86	−0.35 (−0.76, 0.06)	0.09	0.03 (−0.36, 0.41)	0.89
Other/unknown	−0.08 (−0.41, 0.25)	0.63	0.00 (−0.30, 0.30)	0.98	−0.11 (−0.48, 0.25)	0.54	−0.05 (−0.37, 0.28)	0.78
Dialysis vintage, mo	0.13 (0.03, 0.24)	0.01	0.02 (−0.08, 0.12)	0.67	0.12 (0.00, 0.25)	0.06	0.00 (−0.13, 0.12)	0.94
Systolic blood pressure, mm Hg	−0.03 (−0.14, 0.08)	0.54	−0.07 (−0.16, 0.03)	0.20	−0.07 (−0.20, 0.05)	0.25	−0.10 (−0.21, 0.01)	0.08
Body mass index, kg/m^2	0.07 (−0.05, 0.19)	0.23	0.07 (−0.04, 0.18)	0.20	0.11 (−0.03, 0.24)	0.11	0.10 (−0.03, 0.22)	0.12
Albumin, g/dL	0.02 (−0.09, 0.13)	0.73	−0.01 (−0.11, 0.09)	0.89	0.02 (−0.10, 0.14)	0.75	−0.01 (−0.12, 0.10)	0.89
Hematocrit, %	−0.02 (−0.12, 0.09)	0.78	0.01 (−0.09, 0.11)	0.89	−0.03 (−0.15, 0.10)	0.66	−0.01 (−0.12, 0.10)	0.87
Phosphate, mg/dL	0.04 (−0.07, 0.15)	0.47	−0.07 (−0.17, 0.04)	0.20	0.04 (−0.09, 0.17)	0.53	−0.11 (−0.23, 0.01)	0.08
Intact PTH (pg/mL)	0.07 (−0.04, 0.17)	0.22	0.00 (−0.10, 0.10)	0.98	0.04 (−0.09, 0.16)	0.56	−0.04 (−0.15, 0.08)	0.54
White blood cell count, ×10^3/μL	−0.17 (−0.28, −0.07)	0.001	−0.16 (−0.26, −0.06)	0.002	−0.19 (−0.31, −0.08)	0.001	−0.18 (−0.29, −0.07)	0.001

Continued

dialysis patients having performance on the Digit Symbol Substitution Test and Trails A and B >1.5 SDs below general population norms (table 2).

Factors associated with poorer memory defined by PCA. In univariate analyses, older age, male sex, different forms of vascular disease, and higher WBC count were associated with lower levels of memory by PCA score. After adjustment for age, sex, race, and education, only higher WBC count and more depression symptoms as assessed by the CESD were significantly associated with lower memory by PCA score (table 3).

Factors associated with poorer executive function defined by PCA. In univariate analyses, older age, lower levels of education, presence of diabetes, either diabetes or hypertension as the cause of ESRD, lower serum albumin, and various forms of vascular disease were associated with decreased performance on tests of executive function. In analyses adjusting for age, sex, race, and education, a history of diabetes, having diabetes or hypertension as the cause of ESRD, peripheral vascular disease, coronary artery disease, heart failure, and more depression symptoms were all associated with lower executive function (table 4).

Sensitivity analyses. Results were essentially unchanged if those with stroke were excluded (tables 3 and 4, table e-2) and if only those with MMSE score ≥24 were included (table e-3). After excluding 27 individuals with dialysis access in their dominant arm and 47 individuals with information on dominant arm missing, results were essentially unchanged in the remaining 240 participants. Although higher CESD levels were associated with worse executive function, additional adjustment for CESD did not significantly change the importance of other risk factors in adjusted analyses (data not shown). Dialysis vintage had no significant relationship with memory, but vintage was associated with executive function in a model incorporating 2 slopes. That is, below 42 months, longer vintage was associated with worse executive function, whereas beyond 42 months no association with vintage was noted (table 4). Adjustment for dialysis vintage using the 2-slope model did not significantly change the importance of other risk factors in adjusted analyses (data not shown).

DISCUSSION

In this study, we demonstrate a high frequency of cognitive impairment in hemodialysis patients in comparison with general population normative data. Impairment is present despite preserved MMSE scores and is particularly manifest in tasks that reflect executive function domains. Although there are few independent risk factors for the memory component of the cognitive function, the presence of vascular disease risk factors and vascular disease is associated with impairment in domains spanning executive functions.

Table 3 Continued

	All				No stroke			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	β (95 CI)	p Value	β (95 CI)	p Value	β (95 CI)	p Value	β (95 CI)	p Value
CRP, mg/L	−0.07 (−0.13, −0.01)	0.02	−0.02 (−0.07, 0.04)	0.56	−0.07 (−0.14, −0.01)	0.03	−0.02 (−0.08, 0.04)	0.53
spKt/V	0.01 (−0.10, 0.12)	0.87	−0.10 (−0.20, 0.01)	0.07	0.01 (−0.11, 0.13)	0.87	−0.10 (−0.22, 0.02)	0.10
CESD	−0.09 (−0.20, 0.01)	0.09	−0.11 (−0.21, −0.02)	0.02	−0.10 (−0.22, 0.02)	0.10	−0.14 (−0.24, −0.03)	0.01

Abbreviations: CESD = Center for Epidemiological Studies Depression Scale; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular disease; GN = glomerulonephritis; PTH = parathyroid hormone; ref. = reference; spKt/V = single-pool Kt/V (a measure of dialysis dose).

[a] Cognitive tests comprising the majority of the memory domain include delayed recall, immediate recall, and recognition, with smaller contributions from other tests. Digit Span, Mental Alternations and Controlled Oral Word Association Test were not included in calculation of the principal component analysis. All β coefficients for continuous variables are per 1-SD increase except for CRP where it is per doubling. Age, sex, education, and race are included in all adjusted models along with a single comorbid condition or laboratory test result.

[b] History of CVD is defined as the presence of peripheral vascular disease or coronary artery disease.

Table 4 Relationship of risk factors to the principal component analysis of executive function score[a]

	All				No stroke			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	β (95 CI)	*p* Value	β (95 CI)	*p* Value	β (95 CI)	*p* Value	β (95 CI)	*p* Value
Age, y	−0.42 (−0.51, −0.33)	<0.0001	−0.46 (−0.55, −0.36)	<0.0001	−0.42 (−0.52, −0.33)	<0.0001	−0.45 (−0.54, −0.35)	<0.0001
Female	−0.05 (−0.26, 0.16)	0.64	−0.07 (−0.25, 0.11)	0.43	−0.03 (−0.26, 0.19)	0.77	−0.04 (−0.23, 0.15)	0.70
African American	0.07 (−0.18, 0.31)	0.59	−0.30 (−0.53, −0.08)	0.01	0.06 (−0.21, 0.33)	0.67	−0.28 (−0.52, −0.05)	0.02
Education, ref. <12th grade								
≥2 y of college	0.83 (0.47, 1.19)	<0.0001	0.71 (0.40, 1.03)	<0.0001	0.91 (0.52, 1.30)	<0.0001	0.76 (0.43, 1.10)	<0.0001
High school graduate	0.65 (0.31, 1.00)	0.0002	0.59 (0.29, 0.89)	0.0002	0.70 (0.32, 1.07)	0.0003	0.61 (0.28, 0.93)	0.0003
Coronary artery disease	−0.58 (−0.78, −0.37)	<0.0001	−0.26 (−0.45, −0.06)	0.01	−0.62 (−0.85, −0.40)	<0.0001	−0.29 (−0.51, −0.08)	0.01
Peripheral vascular disease	−0.47 (−0.70, −0.23)	0.0001	−0.29 (−0.50, −0.07)	0.01	−0.51 (−0.78, −0.24)	0.0002	−0.30 (−0.54, −0.07)	0.01
History of CVD[b]	−0.60 (−0.79, −0.40)	<0.0001	−0.27 (−0.46, −0.07)	0.01	−0.67 (−0.88, −0.46)	<0.0001	−0.32 (−0.53, −0.11)	0.003
Stroke	−0.35 (−0.62, −0.08)	0.01	−0.19 (−0.42, 0.04)	0.11				
Heart failure	−0.45 (−0.66, −0.24)	<0.0001	−0.22 (−0.41, −0.04)	0.02	−0.51 (−0.74, −0.29)	<0.0001	−0.26 (−0.47, −0.06)	0.01
Diabetes	−0.33 (−0.53, −0.13)	0.001	−0.20 (−0.38, −0.02)	0.03	−0.34 (−0.56, −0.12)	0.003	−0.20 (−0.40, −0.01)	0.04
Hypertension	−0.43 (−0.77, −0.09)	0.01	−0.29 (−0.58, 0.00)	0.05	−0.33 (−0.71, 0.05)	0.09	−0.14 (−0.46, 0.18)	0.39
Smoking status, ref. prior								
Smokes currently	−0.18 (−0.54, 0.19)	0.34	−0.31 (−0.63, 0.00)	0.05	−0.10 (−0.51, 0.32)	0.65	−0.22 (−0.58, 0.14)	0.23
Never smoked	0.20 (−0.02, 0.43)	0.07	−0.06 (−0.26, 0.14)	0.55	0.19 (−0.06, 0.43)	0.13	−0.07 (−0.28, 0.14)	0.52
Primary cause of ESRD, ref. GN								
Diabetes	−0.77 (−1.06, −0.48)	<0.0001	−0.47 (−0.74, −0.20)	0.0006	−0.71 (−1.02, −0.41)	<0.0001	−0.42 (−0.69, −0.15)	0.0003
Hypertension	−0.84 (−1.16, −0.51)	<0.0001	−0.44 (−0.74, −0.14)	0.004	−0.87 (−1.22, −0.52)	<0.0001	−0.48 (−0.80, −0.16)	0.0003
Other/unknown	−0.39 (−0.68, −0.09)	0.01	−0.32 (−0.58, −0.06)	0.02	−0.33 (−0.64, −0.02)	0.04	−0.28 (−0.55, −0.01)	0.04
Dialysis vintage <42 mo	−0.12 (−0.22, −0.03)	0.01	−0.13 (−0.21, −0.05)	0.002	−0.12 (−0.22, −0.01)	0.030	−0.12 (−0.21, −0.03)	0.007
Dialysis vintage ≥42 mo	0.08 (0.03, 0.13)	0.002	0.03 (−0.01, 0.07)	0.16	0.08 (0.03, 0.14)	0.005	0.03 (−0.02, 0.08)	0.27
Systolic blood pressure, mm Hg	0.05 (−0.06, 0.15)	0.38	0.03 (−0.06, 0.12)	0.50	0.07 (−0.04, 0.19)	0.22	0.06 (−0.04, 0.15)	0.23
Body mass index, kg/m^2	−0.01 (−0.12, 0.10)	0.86	0.01 (−0.09, 0.11)	0.81	0.02 (−0.10, 0.14)	0.75	0.04 (−0.06, 0.15)	0.42
Albumin, g/dL	0.13 (0.03, 0.23)	0.01	0.07 (−0.02, 0.16)	0.12	0.14 (0.04, 0.25)	0.01	0.08 (−0.01, 0.17)	0.09
Hematocrit, %	0.00 (−0.10, 0.11)	0.95	0.02 (−0.07, 0.10)	0.71	0.00 (−0.11, 0.11)	0.98	0.02 (−0.07, 0.11)	0.68
Phosphate, mg/dL	0.09 (−0.02, 0.19)	0.10	0.00 (−0.09, 0.09)	0.99	0.12 (0.00, 0.23)	0.04	0.01 (−0.09, 0.11)	0.84
Intact PTH, pg/mL	−0.01 (−0.11, 0.08)	0.79	−0.04 (−0.12, 0.04)	0.36	−0.02 (−0.13, 0.09)	0.78	−0.03 (−0.13, 0.06)	0.48

Continued

Table 4 Continued

	All				No stroke			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	β (95 CI)	p Value	β (95 CI)	p Value	β (95 CI)	p Value	β (95 CI)	p Value
White blood cell count, $\times 10^3/\mu L$	0.01 (−0.10, 0.11)	0.89	0.03 (−0.06, 0.12)	0.47	0.01 (−0.10, 0.12)	0.90	0.04 (−0.05, 0.14)	0.40
CRP, mg/L	−0.07 (−0.13, −0.02)	0.01	−0.02 (−0.07, 0.03)	0.37	−0.07 (−0.13, −0.01)	0.03	−0.02 (−0.07, 0.03)	0.49
spKt/V	0.00 (−0.10, 0.11)	0.98	−0.02 (−0.11, 0.08)	0.70	−0.01 (−0.12, 0.10)	0.90	−0.04 (−0.14, 0.06)	0.42
CESD	−0.11 (−0.21, −0.01)	0.04	−0.11 (−0.20, −0.03)	0.01	−0.11 (−0.22, −0.00)	0.04	−0.12 (−0.21, −0.03)	0.01

Abbreviations: CESD = Center for Epidemiological Studies Depression Scale; CI = confidence interval; CVD = cardiovascular disease; CRP = C-reactive protein; GN = glomerulonephritis; PTH = parathyroid hormone; ref. = reference; spKt/V = single-pool Kt/V (a measure of dialysis dose).

[a] Cognitive tests comprising the majority of the executive function domain include Trail Making Tests A and B, Digit Symbol Substitution, and Block Design, with smaller contributions from other tests. Digit Span, Mental Alternation and Controlled Oral Word Association Test were not included in calculation of the principal component analysis. All β coefficients for continuous variables are per 1-SD increase except for CRP where it is per doubling and dialysis vintage where it is per 1-month increase. Age, sex, education, and race are included in all adjusted models along with a single comorbid condition or laboratory test result.

[b] History of CVD is defined as the presence of peripheral vascular disease or coronary artery disease.

This is one of the largest studies of which we are aware that has evaluated detailed measures of cognitive function in hemodialysis patients. Our results confirm prior studies that have demonstrated a high prevalence of cognitive impairment in this population.[3,20–22] In one study, the MMSE was administered to 336 dialysis patients: 22% of subjects had mild impairment (MMSE scores 18–23) and 8% had moderate-severe impairment (MMSE scores 0–17).[3] In another study evaluating 338 hemodialysis patients, 14% were classified with mild impairment, 36% with moderate impairment, 37% with severe impairment, and 13% with normal cognition. Cognitive impairment was associated with low education, higher Kt/V, and a history of stroke.[22] In the Frequent Hemodialysis Network, impaired executive function, defined by failure to complete the Trail Making B task within 5 minutes, was common among hemodialysis patients but was not strongly associated with patient or dialysis-associated factors.[21] Our study substantially adds to these by performing detailed cognitive testing, focusing on both memory and executive function, evaluating a wide range of risk factors for each form of cognitive impairment, and comparing the results to validated normative data. We also demonstrate that, even among those with MMSE score ≥24, there is a high frequency of more subtle degrees of cognitive impairment. Previously, in a pilot study of 25 dialysis patients, we noted that despite preserved MMSE score (≥24), hemodialysis patients had significant cognitive impairment.[23] We have now extended this result to a much larger and more generalizable population. Patients on average had preserved premorbid verbal IQ (as ascertained by the North American Adult Reading Test), suggesting that the declines in cognitive function likely occurred through the course of their illness.

This study does not demonstrate that dialysis per se is a risk factor for cognitive impairment, but rather that dialysis patients (even those with preserved MMSE score) have a high frequency of poor performance on cognitive testing. The only way the former question could be addressed is by having a control group of individuals who do not have kidney disease but have a similar prevalence of vascular disease and vascular risk factors as dialysis patients. We are not aware of large studies performing similar cognitive tests that meet these inclusion criteria.

Executive function seems to be affected to a greater extent than memory in dialysis patients. The latter is consistent with the hypothesis that vascular disease, whether due to atherosclerosis or arteriosclerosis, may be the primary cause of cognitive impairment in this population. The finding that risk factors for poorer executive function include vascular disease itself and risk factors for vascular disease supports this hypothesis. We had previously demonstrated that vascular disease, as assessed by either coronary disease or peripheral vascular

disease, is associated with abnormalities in executive function in hemodialysis patients.[24] The current study adds to the latter by including a larger number of individuals, evaluating many potential risk factors for cognitive impairment, providing detailed comparisons with normative data, and incorporating additional cognitive tests that were assessed in nearly half of the study participants.

Our study has several strengths. These include a relatively large cohort focused on cognitive function incorporating detailed ascertainment of both cognitive function as well as its potential risk factors. The study also has several limitations. Although the population is generalizable to the US Renal Data System dialysis population from a demographic, vascular disease prevalence, and laboratory result standpoint,[25] it excludes non-English speakers and acutely ill individuals, and includes participants who, overall, are more educated than the US ESRD population.[3,26,27] Our cohort consisted of patients who were on dialysis for less time than the US ESRDS population. Although longer vintage was associated with worse executive function in the first 42 months of dialysis, after 42 months there was no significant relationship. The relationship of vintage with cognitive function likely is affected by survival bias. Given the exclusion of acutely ill individuals and those with severe baseline dementia, the frequencies of cognitive impairment in our study likely underestimate the true prevalence of cognitive impairment among hemodialysis patients. Critically, recognition of cognitive impairment and appreciation of the risk factors for early cognitive impairment are important for both future planning as well as implementation of interventions to address cognitive performance in dialysis patients. Although we hypothesize that vascular disease, whether it be macro- or micro-cerebrovascular disease, is the cause of worse performance in executive functioning domains, we do not have imaging studies to confirm this hypothesis. We performed cognitive testing during the dialysis procedure. The dialysis unit can be a noisy environment potentially leading to distractions and the dialysis procedure itself could possibly lead to delirium that affects performance on cognitive tests.[28–33] However, we have recently demonstrated that cognitive performance is not affected by the time of testing. In a randomized crossover study of 40 patients, performance on cognitive testing was no different 1 hour before dialysis vs the first hour of the dialysis treatment.[34] It is also important to recognize that most patient education and contact with medical practitioners occur during dialysis treatments, making this a critical time for communication. Additionally, reflecting the cross-sectional design, determining cause-and-effect relationships is not possible. Finally, we have not evaluated several nontraditional vascular and nonvascular risk factors that may contribute to cognitive impairment.

There are important implications of our results. Health care providers should be aware of the high prevalence of cognitive impairment when providing care to dialysis patients. Given the high prevalence of cognitive impairment in maintenance hemodialysis patients, if possible, important educational interactions and discussions on end-of-life care should be initiated during the earlier stages of kidney disease. Furthermore, health care proxies should be involved in decision-making. One should be cautious in using an MMSE score <24 to screen for cognitive impairment in dialysis patients because many patients with MMSE score ≥ 24 also have more subtle degrees of cognitive impairment. Finally, interventions to decrease vascular disease should be evaluated to reduce the prevalence of cognitive impairment in patients undergoing dialysis.

AUTHOR CONTRIBUTIONS

Mark Sarnak: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. Hocine Tighiouart: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Tammy Scott: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Kristina Lou, Eric Sorensen, and Lena Giang: drafting/revising the manuscript, acquisition of data, study supervision. David Drew: drafting/revising the manuscript. Kamran Shaffi: drafting/revising the manuscript, study supervision. James Strom: drafting/revising the manuscript, analysis or interpretation of data, study supervision. Ajay Singh: drafting/revising the manuscript, contribution of vital reagents/tools/patients, study supervision. Daniel Weiner: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision.

ACKNOWLEDGMENT

The authors acknowledge the tremendous assistance of Dialysis Clinic, Inc. and, in particular, the staff and patients at the 5 DCI units in the Boston area and St. Elizabeth's Dialysis Unit without whose cooperation the study would not have been successful.

STUDY FUNDING

The study was funded by the NIDDK through grants R21 DK068310 (M.J.S.), R01 DK078204 (M.J.S.), and K23 DK71636 (D.E.W.).

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received May 29, 2012. Accepted in final form September 17, 2012.

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