Increased Presence of Cognitive Impairment in Hemodialysis Patients in the Absence of Neurological Events

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Key Words

Cognitive impairment • Chronic kidney disease • Hemodialysis

Abstract

Background/Aims: Cognitive impairment (CI) is highly prevalent among hemodialysis (HD) patients and is associated with increased morbidity and mortality. The aim was to compare cognitive function in HD patients with no history of stroke or dementia and well-matched controls. Studies are required to determine the impact of HD and chronic kidney disease-specific risks on CI. **Methods:** 76 outpatients (50 receiving outpatient HD and 26 with normal kidney function matched for age and comorbidity) underwent a cross-sectional observational study. HD patients were well dialyzed and had optimal hemoglobin levels. A battery of eight neuropsychological tests was used. Outcomes included assessment scores of neurocognitive testing and prevalence and subtype of CI. **Results:** Compared to controls, HD subjects had significantly lower composite scores for each tested cognitive domain. In each domain except memory, the percentage of subjects with impairment was significantly higher in HD subjects than controls. Differences between the groups were independent of vascular and dementia risk fac-

tors. 82% of HD subjects met criteria for CI versus 50% of controls. Non-amnesic subtype of CI was more prevalent in both groups. **Conclusion:** Well-dialyzed HD patients with optimized hemoglobin levels and with no history of stroke or dementia performed significantly worse on multiple measures of cognition compared to controls. A higher prevalence of non-memory impairment may suggest an underlying vascular versus neurodegenerative mechanism. HD and chronic kidney disease-specific risk factors may contribute to early CI not readily detected by routine screening methods.

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Introduction

Studies have shown that the prevalence of cognitive impairment (CI) among hemodialysis (HD) patients is higher than that of the general population [1, 2]. The consequences of CI in HD patients are significant and include increased cost of care, increased mortality, and increased rate of hospitalization [3].

HD patients have multiple traditional cardiovascular risk factors, which are associated with increased risk of CI and dementia in the general population. However,

these risk factors may not fully account for the high prevalence of CI in the HD population. Chronic kidney disease (CKD) severity has been shown to be associated with cognitive decline and dementia independent of traditional vascular risk factors [4, 5]. Furthermore, HD patients score lower on neurocognitive tests when compared to patients with advanced CKD not yet requiring HD [6]. These findings suggest that CKD and/or factors related to HD may be associated with the higher prevalence of CI. Cyclical hemodynamic stress related to HD coupled with extensive vascular disease may accelerate cognitive deficits characteristic of cerebral microvascular disease.

To better understand the potential role of HD in the development of CI, we proposed to study cognition in well-dialyzed, non-demented HD patients with no clinical history of cerebrovascular disease compared with controls matched for age and comorbidity. We hypothesized that the added vascular risks and hemodynamic stressors imposed by the HD process would result in HD patients having lower scores on neurocognitive testing and a higher percentage of CI compared with matched controls.

Participants and Methods

Study Participants

An observational, cross-sectional study of male veterans receiving outpatient HD treatments and general primary care at the James J. Peters VA Medical Center, Bronx, N.Y., was performed. A convenience sample of consecutively encountered individuals was recruited between October 2006 and March 2011. 50 of 100 HD patients were included. For controls, 26 out of approximately 500 non-CKD primary care patients, within the prescribed age range of HD patients, were included. HD participants had to be fluent in English, receiving treatment for at least 3 months and have a 3-month average urea reduction ratio (URR) of $\geq 65\%$ at the time of screening. All HD subjects were dialyzed on a 3-day-per-week schedule for 3–4 h each session according to National Kidney Foundation guidelines [7]. Primary care physicians referred patients from their clinics if they met criteria for entry into the study. All subjects provided written, informed consent per regulations of the local institutional review board. Non-CKD control subjects were included if they had normal renal function defined as an eGFR ≥ 60 ml/min/1.73 m² with or without proteinuria on urinalysis. Control subjects were frequency matched for a history of hypertension (HTN) and/or diabetes mellitus (DM) with the HD subjects. Subjects were excluded if they had chart documentation or knowledge of having a stroke or dementia, a history of Parkinson's disease, other neurodegenerative disease, liver function enzymes (AST and ALT) more than twice the upper limit of normal, or a hemoglobin level <10 g/dl. All subjects underwent neuropsychological testing on a non-dialysis day except for 4 patients; 1 was tested just prior to receiving HD therapy and 3 were tested within an hour after HD therapy.

Medical Chart Review, Laboratory and Cognitive Assessments

Demographic characteristics, educational levels, and chronic health conditions were obtained from patients' electronic medical records. All patients, as part of annual clinical care, were screened for depression using the Patient Health Questionnaire-2 (PHQ-2) [8]. For controls, laboratory values for hemoglobin, creatinine, liver function tests, and hemoglobin A_{1c} were recorded within 6 months of neuropsychological testing. Laboratory values from HD patients included hemoglobin, calcium (Ca), serum phosphorus (PO₄), parathyroid hormone intact (PTHi) and blood urea nitrogen (BUN) for URR calculation. As part of routine clinical care, these labs are drawn monthly on dialysis days prior to the treatment. Values for Ca, PO₄, PTHi and URR were calculated by averaging the monthly labs for 3 consecutive months prior to neuropsychological testing. All tests were performed at a single central laboratory using standard methods. Blood draws were completed within 1 week of neurocognitive testing for homocysteine, and C-reactive protein (CRP). Blood pressure measurements were taken from the day of neuropsychological testing.

A battery of eight validated neuropsychological tests was administered to all study participants. The neuropsychological battery included: the Mini-Mental State Examination (MMSE), the California Verbal Learning Test-II (CVLT-II) Standard Form, the Controlled Oral Word Association Test (COWAT-FAS), animal category fluency, Digit Span, the Symbol Digit Modality Test (SDMT), Trails A & B, and the Stroop Word & Color tests. Results of neurocognitive tests were used to classify subjects with CI subtype by using diagnostic criteria utilized from the Cardiovascular Health Cognition Study and the Mayo Clinic Study of Aging as approximate guidelines [9–11]. Subjects with a composite score for long and short delay memory tests ≥ 1.5 standard deviations (SD) below age-matched norms were classified as CI amnesic type. Study participants who did not meet criteria for CI amnesic type, but scored ≥ 1.5 SD below the norm on two or more tests in a non-memory domain (Attention/Processing Speed, Executive Function, or Language), were classified as CI non-amnesic type.

Statistical Analysis

For between-group comparisons on each cognitive test, raw scores were converted to age- and education-standardized T scores. T scores ≥ 1.5 SD below the mean were identified as impaired. To calculate the domain composite T scores, a mean T score of all the completed cognitive tests within each particular domain was calculated for each subject. Next, all subjects' individual domain composite scores were averaged within each group to calculate the overall domain composite score for either control or HD groups. Descriptive statistics are reported as mean $\pm$ SD or percent as appropriate. Independent sample t tests were used to evaluate differences between control and HD groups on individual cognitive test T scores and domain composite T scores. Control and HD groups were compared on the demographic and clinical variables represented as a continuous number by using t tests. Multiple regression, two-factor analysis of variance (ANOVA), and logistic regression models were used to adjust for differences between control and HD groups for the following comorbidities: DM, HTN, hyperlipidemia, coronary artery disease, and peripheral vascular disease. A new composite variable for comorbidity was created. Each comorbidity was assigned a single point value. Comorbidity totals for subjects in either group were determined, thus a subject could have 0–5 points assigned for their comorbid-

Table 1. Characteristics of study participants

	Control (n = 26) mean $\pm$ SD (min–max)	HD (n = 50) mean $\pm$ SD (min–max)	p	Power (α 0.05)
Age, years	64 $\pm$ 10 (38–84)	63 $\pm$ 10 (43–84)	0.9	0.06
Education, years	14 $\pm$ 3 (10–22)	13 $\pm$ 2 (9–18)	0.08	0.4
Body mass index	29.0 $\pm$ 4.9 (19.4–43.4)	28.0 $\pm$ 5.6 (19.2–42.2)	0.5	0.1
Years on dialysis	0 (N/A)	2.5 $\pm$ 3.8 (0.3–21)		
Urea reduction ratio (%)	N/A	71 $\pm$ 4 (65–82)		
Ethnicity, n (%)			0.3	
African-American	12 (46)	31 (62)		
Caucasian	5 (19)	10 (20)		
Other	9 (35)	9 (18)		
Marital status			0.008	
Married	13 (52)	10 (20)		
Other	12 (48)	40 (80)		
Traditional cardiovascular risk factors				
Hypertension	22 (85)	46 (92)	0.4	
Diabetes	18 (69)	26 (52)	0.2	
Hyperlipidemia	15 (58)	24 (48)	0.5	
Systolic blood pressure, mm Hg	134 $\pm$ 19	135 $\pm$ 22	0.9	0.04
Diastolic blood pressure, mm Hg	74 $\pm$ 10	72 $\pm$ 13	0.5	0.1
Hemoglobin A _{1C} , %*	7.3 $\pm$ 1.7	6.0 $\pm$ 1.1	<0.001	0.9
Other cardiovascular & cognitive risk factors				
Homocysteine, mg/l*	1.88 $\pm$ 0.55 (1.12–2.88)	3.95 $\pm$ 1.30 (1.5–7.14)	<0.001	0.9
C-reactive protein, mg/l*	8.7 $\pm$ 12.3 (0.6–42.3)	9.4 $\pm$ 13.5 (0.6–69.6)	0.8	0.04
Hemoglobin, g/dl	14.1 $\pm$ 1.0 (12.5–15.9)	11.5 $\pm$ 1.1 (10.0–13.9)	<0.001	0.9

* Hemoglobin A_{1C}: control n = 22, HD n = 50; Homocysteine: control n = 23, HD n = 49; C-reactive protein: control n = 24, HD n = 42.

ity status. Hemoglobin, CRP, and homocysteine were also adjusted for in a separate multiple regression model. For the dichotomous or categorical variables, χ^2 tests were used to determine the significance of differences in prevalence between the groups. The statistical analyses were performed using StatView (SAS, 1998). Because the sample sizes between the two groups (HD, control) were uneven, a harmonic mean was calculated for the sample size [12]. Statistical power calculations were performed for each outcome variable using the Simple Interactive Statistical Analysis website [www.quantitativeskills.com/sisa/].

Results

Baseline Characteristics

Seventy-six male subjects participated in the study, 26 controls and 50 receiving HD. There were no significant differences in demographic variables between the groups (table 1). HTN, DM, hyperlipidemia, peripheral vascular disease, and coronary artery disease were highly prevalent in both groups, with no significant difference between groups. On average, subjects in the HD group dem-

onstrated significantly lower hemoglobin and higher homocysteine than those in the control group (table 1).

All subjects scored ≥ 26 on the MMSE. All subjects screened negative on the PHQ-2. One subject from each group did not complete the Stroop Color & Stroop Color-Word test secondary to color vision deficiency and these tests were not included for those 2 patients.

T Scores for Individual Tests

The results for cognitive tests for each domain in HD and control groups are reported (table 2). The HD group scored ≥ 1.5 SD below the norm on three out of the five measures of attention and processing speed. On measures of executive function, the HD group scored ≥ 1.5 SD below the norm on one measure. The HD group performed best on measures of memory (table 2).

By group comparison, HD subjects scored significantly lower than controls on four of five measures of attention and processing speed. The HD group scored significantly lower than controls on all measures of language, executive function, and memory. These group differenc-

Table 2. Cognitive function T scores by group

Test	Control	HD	p	Power α 0.05	p* (comorbidity adjustment)
Attention and processing speed domain					
Trails A ^a	42 $\pm$ 13	34 $\pm$ 12	0.02	0.7	0.01
Digit span ^a	46 $\pm$ 7	44 $\pm$ 8	0.1	0.2	0.1
Symbol digit modality test ^b	46 $\pm$ 11	38 $\pm$ 10	<0.001	0.5	<0.001
Stroop Word ^b	36 $\pm$ 10	31 $\pm$ 10	0.04	0.5	0.03
Stroop Color ^b	38 $\pm$ 9	32 $\pm$ 10	0.02	0.7	0.01
Executive function domain					
Trails B ^a	41 $\pm$ 14	32 $\pm$ 14	0.007	0.7	0.008
Stroop Color-Word ^b	45 $\pm$ 7	39 $\pm$ 8	0.008	0.9	0.008
Language domain ^b					
Controlled oral word association test (FAS)	48 $\pm$ 7	39 $\pm$ 9	<0.001	0.9	<0.001
Animal naming	49 $\pm$ 10	41 $\pm$ 9	<0.001	0.9	<0.001
Memory domain ^a					
CVLT total recall	51 $\pm$ 11	43 $\pm$ 7	<0.001	0.9	<0.001
CVLT short delay recall	50 $\pm$ 13	43 $\pm$ 10	0.01	0.7	0.01
CVLT long delay recall	51 $\pm$ 13	44 $\pm$ 8	0.008	0.8	0.009
CVLT long delay recognition	54 $\pm$ 7	42 $\pm$ 13	<0.001	0.9	<0.001

All tests total control n = 26, HD n = 50 except the following: Stroop Color, Stroop Color-Word: control n = 25, HD n = 49.

* p values adjusted for diabetes, hypertension, hyperlipidemia, coronary artery disease, and peripheral vascular disease.

^a Age-adjusted.

^b Age- and education-adjusted (T scores).

Table 3. Composite domain T scores and percent impairment

Domain	Control	HD	p	Power α 0.05	p* (comorbidity adjustment)
Attention and processing speed	42 $\pm$ 7	36 $\pm$ 7	<0.001	0.9	<0.001
Impaired (%)	6 (23)	25 (50)	0.03		0.02
Executive function	42 $\pm$ 10	36 $\pm$ 9	0.004	0.7	0.005
Impaired (%)	3 (12)	24 (48)	0.002		<0.001
Language	49 $\pm$ 6	40 $\pm$ 7	<0.001	0.9	<0.001
Impaired (%)	0	15 (30)	0.002		<0.001
Memory	51 $\pm$ 10	43 $\pm$ 7	<0.001	0.9	<0.001
Impaired (%)	1 (4)	6 (12)	0.4		0.2

* p values adjusted for diabetes, hypertension, hyperlipidemia, coronary artery disease, and peripheral vascular disease.

es remained significant after controlling for comorbidities. Years on dialysis mildly correlated with T scores for one test of language, the COWAT-FAS ($r = 0.35$, $p = 0.01$).

Composite T Scores and Prevalence of Cognitive Impairment by Domain

Composite T scores for each cognitive domain and the prevalence of impairment for HD and control groups are reported (table 3). The HD group had significantly lower

composite T scores for each domain tested when compared to controls. HD patients demonstrated a significantly higher percentage of impairment in attention and processing speed, executive function, and language versus the control group. These group differences remained significant after controlling for comorbidities. The percentage of patients meeting criteria for memory impairment was not significantly different between the groups and memory was the least impaired domain in HD pa-

Fig. 1. CI by group and subtype.

tients (12%). There was no correlation between composite scores and years on dialysis.

Other Vascular and Cognitive Risk Factors

In the HD group, there were no significant correlations between cognitive performance and any of the following: PTHi level, PO_4 , or Ca/PO_4 product. Controlling for hemoglobin, homocysteine, and CRP levels, significant differences between groups remained on all measures and domains.

Prevalence and Subtype of CI

A flow chart of prevalence and subtype of CI is presented (fig. 1). Criteria for CI were met in 82% of HD and 50% of control subjects. Of HD and control subjects who met criteria for CI, the non-amnestic subtype was more prevalent than the amnestic subtype in each group (78 vs. 22% HD; 77 vs. 23% controls) (fig. 1).

Discussion

Compared to matched controls without CKD, well-dialyzed HD subjects with no history of dementia or stroke scored significantly lower on multiple measures of cognition and had a higher percentage of CI in each tested domain except for memory. Despite all subjects having an $\text{MMSE} \geq 26$, 82% of HD subjects met criteria for CI versus 50% for control subjects. These findings suggest that the high prevalence of CI in HD patients may not be entirely explained by a heavy burden of cardiovascular risk factors.

A high prevalence of CI exists among patients receiving HD therapy [1, 2, 13]. Although some studies show a relationship between cognitive function and eGFR inde-

pendent of traditional cardiovascular risk factors [4, 5], the HD population has mainly been compared to the general population with a lower prevalence of DM, HTN, hyperlipidemia and stroke. The strength of our findings is that we tested well-dialyzed, non-demented HD patients with no clinical history of stroke or cerebrovascular disease, therefore minimizing the influence of uremia, established dementia, and cerebrovascular damage on the results of neurocognitive testing. Furthermore, our control subjects were selected from a similar population to our HD subjects, lessening the differences attributable to cardiovascular risk factors. The findings from this study are consistent with a growing body of evidence that CKD and the HD process may be independent contributors to the high prevalence of CI in this population.

HD patients have high rates of white matter hyperintensities on magnetic resonance imaging [14, 15], and white matter disease correlates more closely with deficits in executive function and attention/mental processing speed than with deficits within the memory domain [16, 17]. In this study, the CI subtype in both HD patients and controls was predominantly non-amnestic. Additionally, HD subjects scored better on all tests of memory compared to other domains and memory was the only domain where HD subjects did not have a significantly greater percent impairment versus controls. This pattern of neurocognitive deficits has been observed in similar studies of HD patients and suggests an underlying vascular mechanism [1, 18]. Even though the HD subjects did not have a clinical history of stroke, neuroimaging was not available to exclude preexisting silent cerebrovascular lesions as a potential etiology for our cognitive findings. Several factors in HD patients are likely to increase the risk of developing white matter lesions.

Evidence suggests that white matter lesions on magnetic resonance imaging are related to hypoperfusion in the setting of microvascular disease [19]. The hemodynamic alterations associated with HD may play a role in the development of white matter disease. During each dialysis session, volume removal can range from 3 to 4 liters over the course of 4 h. Reductions in middle cerebral artery blood velocity after HD have been shown to correlate with the volume of fluid removed during the treatment [20]. Progression of cerebral atrophy in HD patients has been associated with hypotensive episodes on HD and number of years receiving HD [21, 22]. A progressive decline in white matter and frontal lobe blood flow based on years of HD are likely to contribute to the pathogenesis of ischemic cerebral damage in HD patients [23]. While HD is lifesaving, the combination of long-term cyclical hemodynamic stress with existing cerebral small vessel disease may be an important contributor to the high prevalence of silent ischemic cerebrovascular disease and characteristic cognitive deficits in these patients.

While subclinical ischemic cerebrovascular disease likely plays a major role in the pathogenesis of CI in HD subjects, other CKD-specific risk factors are potential contributors. In this study, PTHi, Ca, PO₄, CRP, hemoglobin, and homocysteine levels were not associated with cognitive performance in the HD population.

Although efforts were made to exclude and control for the multiple causes of CI in the HD group, our study has limitations. Our study had a relatively small number of subjects and although stroke was excluded by history and medical record review, neuroimaging was not available. In addition, all of our subjects were male, which limits generalization of our findings to female patients. Another

possible limitation may have been in the diagnosis of CI based on neurocognitive scores in the absence of a subjective clinical complaint of memory or cognitive decline. Due to the cross-sectional design of this study, our observations are at best hypothesis generating.

The prevalence of CI in HD patients is high and is associated with poor outcomes. While the mechanism is likely to be multifactorial, efforts to more clearly define the role of the HD process itself or factors specific to CKD are critical. Increasing HD frequency is associated with improved blood pressure and serum phosphorus control [24] which may attenuate the hemodynamic stress and rate of atherosclerosis in this population. While more frequent HD may not improve cognition, early initiation of such treatments may help lower the incidence of CI by reducing cerebrovascular risk burden. Future studies should evaluate the effect of dialysis modality, frequency, and duration of treatment on cognitive function. Neuroimaging studies in combination with cognitive measures are required to further explain the mechanisms for early CI in patients receiving HD.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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