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Original Investigation

Cognitive Decline and Its Risk Factors in Prevalent Hemodialysis Patients

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Background: Cognitive impairment is common in patients treated with hemodialysis. The trajectory of cognitive function and risk factors for cognitive decline remain uncertain in this population.

Study Design: Longitudinal cohort.

Setting & Participants: 314 prevalent hemodialysis patients.

Predictors: Age, sex, race, education level, hemodialysis vintage, cause of end-stage renal disease, and baseline history of cardiovascular disease.

Outcomes: Cognitive function as determined by a comprehensive neurocognitive battery, administered at baseline and yearly when possible. Individual cognitive test results were reduced into 2 domain scores using principal components analysis, representing memory and executive function, which were used as our coprimary outcomes and by definition have a mean of zero and SD of 1.

Results: Mean age was 63 years; 54% were men, 22% were black, and 90% had at least a high school education. During a median follow-up of 2.1 (IQR, 0.9-4.2) years, 196 had at least 1 follow-up test, 156 died, and 43 received a kidney transplant. Linear mixed models and joint models, which accounted for competing risks from death, dropout, or kidney transplantation, showed nearly identical results. The joint model demonstrated a decline in executive function (−0.09 [95% CI, −0.13 to 0.05] SD per year), whereas memory improved slightly (0.05 [95% CI, 0.02 to 0.08] SD per year). A significant yearly decline was also seen in the Mini-Mental State Examination score (median change, −0.41; 95% CI, −0.57 to −0.25). Older age was the only significant risk factor for steeper executive function decline (−0.04 [95% CI, −0.06 to −0.02] SD steeper annual decline for each 10 years of age).

Limitations: Prevalent hemodialysis patients only, limited follow-up testing due to high mortality rate, and exclusion of participants with severe cognitive deficits or dementia.

Conclusions: Prevalent hemodialysis patients demonstrate significant cognitive decline, particularly within tests of executive function. Older age was the only statistically significant risk factor for steeper cognitive decline, which may have important clinical consequences for patient management and education. Future studies should evaluate strategies to maintain or improve cognitive function.

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INDEX WORDS: Cognitive impairment; hemodialysis; memory; executive function; neurocognitive battery; cognitive decline; risk factor; end-stage renal disease (ESRD); disease progression; cardiovascular disease (CVD); kidney disease cerebrovascular neuropathology.

Cognitive impairment is common and frequently marked in patients with end-stage renal disease (ESRD) treated with dialysis, with prevalence rates of moderate cognitive impairment estimated at 30% to 60%.[1-3] Notably, cognitive impairment contributes to increased morbidity and mortality.[3,4] A recent meta-analysis that incorporated many prior studies of cognitive function in patients with kidney disease confirmed poor cognitive performance in those receiving hemodialysis.[5] However, because most of these prior studies in dialysis patients are cross-sectional, it remains unclear whether there is significant decline in cognitive function over time, and if so, how rapidly.

Previous longitudinal studies of dialysis patients are limited by a small number of participants and a

limited array of cognitive tests.[6-8] Accordingly, there is uncertainty as to whether certain types of cognitive function, such as memory or executive function, decline at different rates. In particular, executive function, which broadly includes attention and planning, may decline faster because its pathophysiology is tied to cerebrovascular disease,[9] a common finding in hemodialysis patients. Finally, though well established in the general population,[10] it is important to establish what risk factors, including dialysis-specific risk factors, are associated with worsening cognition[1,4,11] because this knowledge is needed to implement strategies to limit cognitive decline in this vulnerable population.

We therefore assessed cognitive function using a comprehensive battery of cognitive tests at baseline and then yearly in a cohort of maintenance hemodialysis patients. We evaluated for cognitive decline and also explored risk factors for decline, focusing additionally on memory and executive function cognitive domains.[2,12] Our prespecified hypotheses, based on cross-sectional data,[2,12] was that due to progression of vascular disease, executive function would decline more than memory and that older age and a baseline history of cardiovascular disease (CVD) would be risk factors for steeper decline.

METHODS

Study Population

Outpatients 18 years or older receiving maintenance in-center hemodialysis at 5 Dialysis Clinic Inc units and 1 hospital-based outpatient unit (St. Elizabeth's Medical Center) in the greater Boston area were screened for the Cognition and Dialysis Study, with study enrollment occurring from January 28, 2004, through May 31, 2012.[2] Eligibility criteria included English fluency and sufficient visual and hearing acuity needed to complete neurocognitive testing. To minimize floor effects and reflecting inability to provide informed consent, individuals with Mini-Mental State Examination (MMSE) scores ≤10 and/or advanced dementia based on medical record review were excluded. Temporary exclusion criteria included non−access-related hospitalization within 1 month of screening, receipt of hemodialysis for less than 1 month, and single-pool Kt/V (spKt/V) < 1.0. The Tufts Medical Center/Tufts University Institutional Review Board approved this study (IRB# 6409), and all participants who completed the detailed cognitive testing signed informed consent. The clinical and research activities reported are consistent with the Declaration of Helsinki.

Baseline Demographics and Clinical Characteristics

Demographic, clinical, and laboratory factors were ascertained at the time of cognitive testing. Education information (<12th grade, high school graduate to <2 years of college, and ≥2 years of college) was obtained via patient questionnaire. History of CVD, defined as a composite of either coronary artery disease and/or peripheral vascular disease, was determined by patient history or documentation in the patient's electronic or paper chart. Patients were queried about a personal history of myocardial infarction and coronary revascularization, which were used to define coronary disease, and intermittent claudication and peripheral vascular disease, which were used to define peripheral vascular disease.

Additionally, Dialysis Clinic Inc electronic medical and paper records were reviewed for a history of these conditions, with specific focus on problem lists, hospital discharge summaries, cardiac test results, and procedure results. Additional medical history, including primary cause of ESRD, hemodialysis vascular access type, and dialysis vintage (time since hemodialysis therapy initiation), were obtained from the Dialysis Clinic Inc or St. Elizabeth's electronic record, as were mean monthly systolic and diastolic blood pressures and body mass index. Serum albumin level and spKt/V most proximate to the time of cognitive testing were obtained from participant medical records.

Neurocognitive Assessment

At study enrollment, participants were administered a battery of neurocognitive tests by research coordinators after a period of training and direct observation by the study neuropsychologist (T.S.). The same battery of tests was administered yearly to study participants when possible. To maintain quality and inter-rater reliability, testing was observed by the study neuropsychologist at 3- to 6-month intervals. To limit participant fatigue, all testing was completed during the first hour of hemodialysis. Using the same battery of tests, we have previously demonstrated similar performance regardless of whether testing was performed during the first hour of dialysis or before the start of a dialysis session.[13] When possible, neurocognitive testing was performed in a private room or in as quiet an environment as possible. The neurocognitive battery included well-validated commonly used cognitive tests (Table S1, available as online supplementary material) that possess high inter- and intrarater reliability. The MMSE[14] was used as a screening test. The neurocognitive battery consisted of the Wechsler Memory Scale, third edition; Word List Learning Subtest[15]; Wechsler Adult Intelligence Scale, third edition; Block Design[15] and Digit Symbol-Coding Subtests[15]; and Trail-Making Test, parts A and B[16] (Trails A and B). For Trails B, a 300-second time limit was imposed, with those unable to complete the test during this time considered noncompleters. In year 3 of the study, the cognitive panel was expanded to include additional verbal tests assessing both memory and executive functions, including Digit Span (forward and backward),[15] the Mental Alternation Test,[17] and the Controlled Oral Word Association Test.[18]

Our prespecified primary outcomes were change in memory and executive function over time, with risk factors for decline examined as exploratory analyses. Principal component analysis with varimax rotation was used as a data reduction technique with 292 participants to derive composite scores for separate cognitive domains (memory or executive function) in the entire study population.[19] For 18 individuals who were missing baseline 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. Two principal components with eigenvalues greater than 2 were obtained (component 1 eigenvalue, 2.87; component 2 eigenvalue, 2.29), and the resulting component scores subsequently were used as coprimary outcomes. Using this method, all component scores have a mean of zero and standard deviation (SD) of 1. The first component was interpreted to reflect executive functioning, attention, and processing speed (referred to as executive function in the Results section), with the Trails A and B, Block Design, and Digit Symbol-Coding tests contributing significantly (Table S1). The second component primarily was composed of Word List Learning Recall and Recognition and was interpreted to reflect memory. Component loadings for deriving the principal component score at the baseline examination (n = 292) were used to calculate principal component scores for follow-up testing, which included 8 patients who did not have enough data to calculate principal component analysis scores at baseline, bringing the number of unique participants up to 300.