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Original Investigation

Cognitive Function and All-Cause Mortality in Maintenance Hemodialysis Patients

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Background: Cognitive impairment is common in hemodialysis patients and is associated with significant morbidity. Limited information exists about whether cognitive impairment is associated with survival and whether the type of cognitive impairment is important.

Study Design: Longitudinal cohort.

Setting & Participants: Cognitive function was assessed at baseline and yearly using a comprehensive battery of cognitive tests in 292 prevalent hemodialysis patients.

Predictor: Using principal component analysis, individual test results were reduced into 2 domain scores, representing memory and executive function. By definition, each score carried a mean of 0 and SD of 1.

Outcomes: Association of each score with all-cause mortality was assessed using Cox proportional hazards models adjusted for demographics and dialysis and cardiovascular (CV) risk factors.

Results: Mean age of participants was 63 years, 53% were men, 23% were African American, and 90% had at least a high school education. During a median follow-up of 2.1 (IQR, 1.1-3.7) years, 145 deaths occurred. Each 1-SD better executive function score was associated with a 35% lower hazard of mortality (HR, 0.65; 95% CI, 0.55-0.76). In models adjusting for demographics and dialysis-related factors, this relationship was partially attenuated but remained significant (HR, 0.81; 95% CI, 0.67-0.98), whereas adjustment for CV disease and heart failure resulted in further attenuation (HR, 0.87; 95% CI, 0.72-1.06). Use of time-dependent models showed a similar unadjusted association (HR, 0.62; 95% CI, 0.54-0.72), with the relationship remaining significant after adjustment for demographics and dialysis and CV risk factors (HR, 0.79; 95% CI, 0.66-0.94). Better memory was associated with lower mortality in univariate analysis (HR per 1 SD, 0.82; 95% CI, 0.69-0.96), but not when adjusting for demographics (HR, 1.00; 95% CI, 0.83-1.19).

Limitations: Patients with dementia were excluded from the full battery, perhaps underestimating the strength of the association.

Conclusions: Worse executive function and memory are associated with increased risk of mortality. For memory, this association is explained by patient demographics, whereas for executive function, this relationship may be explained in part by CV disease burden.

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INDEX WORDS: Cognition; cognitive impairment; executive function; memory; neurocognitive testing; cardiovascular disease; mortality; hemodialysis; end-stage renal disease (ESRD).

Cognitive impairment is common in patients treated with maintenance hemodialysis.[1,2] Reflecting an aging dialysis population with increased comorbid conditions, the burden of cognitive impairment in the dialysis population may continue to increase, potentially affecting various areas of patient care, such as patient adherence to treatment plans and quality of life.[3,4] Hemodialysis patients have impairment in multiple domains of cognitive function, although executive function, which is critical to planning and carrying out tasks, appears to be more affected than other domains, such as memory.[5] Although the cause of cognitive impairment in dialysis patients appears to be multifactorial,[1] cerebrovascular disease likely is an important cause[6] because cerebrovascular disease more often affects brain structures related to executive function.[7]

Mortality among dialysis patients is high, in part due to the high prevalence of comorbid conditions, including cardiovascular disease (CVD).[8] In individuals without kidney disease, cognitive impairment is associated

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independently with increased mortality,[9,10] with both executive and memory dysfunction contributing to the increased risk.[11,12] Advanced dementia, classified based on administrative codes or medical chart review and therefore likely identifying only individuals with severe disease, also is a risk for increased mortality in dialysis patients.[13,14] However, few studies have explored whether more moderate deficits in cognitive function are associated with mortality in hemodialysis patients and, if so, whether memory, executive function, or both are complicit.

Therefore, we assessed cognitive performance using a detailed neurocognitive battery of tests that maps to multiple cognitive domains and examined the association between cognitive performance and mortality in a cohort of prevalent maintenance hemodialysis patients.

METHODS

Patient Characteristics

Outpatients 18 years or older receiving maintenance 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,[1] with study enrollment occurring from January 28, 2004, through May 31, 2012. Reflecting the nature of the cognitive test battery, eligibility criteria included English fluency and sufficient visual and hearing acuity to complete neurocognitive testing. To minimize floor effects and reflecting inability to provide consent, individuals with Mini-Mental State Examination (MMSE) score of 10 or lower and/or advanced dementia based on medical record review were excluded. Temporary exclusion criteria included non–access-related hospitalization within 1 month, receipt of hemodialysis for less than 1 month, and single-pool Kt/V < 1.0. The Tufts Medical Center/Tufts University Institutional Review Board approved the study, and all participants who completed the detailed cognitive testing signed informed consent.

Baseline Demographics and Clinical Characteristics

Demographic, clinical, and laboratory factors were ascertained at the time of cognitive testing. Demographic data (age, sex, and race) were obtained by participant report, medical charts, and the DCI and St. Elizabeth's Medical Center databases. Education ($<$12th grade, high school graduate to $<$2 years of college, and $\geq$2 years of college) was obtained by patient questionnaire. Medical history, including history of CVD (a composite of either coronary artery disease and/or peripheral vascular disease), stroke, heart failure, diabetes, hypertension, and smoking, was defined 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, DCI 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. Similarly, stroke was defined using patient history or documentation in the patient's electronic or paper chart. Cause of end-stage renal disease and dialysis vintage were obtained from the DCI or St. Elizabeth's electronic record, as were mean monthly systolic and diastolic blood pressures and body mass index. Medication lists from the time of cognitive testing were obtained from DCI electronic records. Predialysis blood tests included serum albumin, hematocrit, phosphorus, and white blood cell count. Single-pool Kt/V was calculated using pre- and postdialysis serum urea nitrogen. All DCI laboratory tests were measured in a central laboratory in Nashville, TN.

Neurocognitive Assessment

At study enrollment, participants were administered a battery of cognitive tests by research assistants after 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. Additionally, in a prior study using the same battery of tests, we demonstrated similar performance regardless of whether testing was performed during the first hour of dialysis or before the start of a dialysis session.[15] 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 that possess high inter- and intrarater reliability and often have established age-, sex-, and/or education-matched normative scores. The MMSE[16] was used as a screening test and the North American Adult Reading Test (NAART) served as a measure of premorbid verbal IQ.[17] The neurocognitive battery consisted of the Wechsler Memory Scale III (WMS-III) Word List Learning Subtest,[18] the Wechsler Adult Intelligence Scale III (WAIS-III) Block Design[18] and Digit Symbol-Coding Subtests,[18] and Trail Making Tests A and B[19] (Trails A and B). For the Trails B test, a 300-second time limit was imposed, with those unable to complete the test during this period considered "noncompleters." 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 (forward and backward),[18] the Mental Alternation Test,[20] and the Controlled Oral Word Association Test (COWAT).[21] 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.

Principal component analysis with varimax rotation was used as a data reduction technique to derive composite scores for separate cognitive domains in the entire study population.[22] For 14 individuals with missing scores on one cognitive test (up to 2 scores if derived from the same test), imputation was performed, incorporating linear regression models based on results of the available cognitive tests. These results were incorporated into the data for principal components analysis. Two principal components with eigenvalues greater than 2 were obtained, and the resulting component scores subsequently were used for primary statistical analyses. Using this method, all component scores have a mean of 0 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, available as online supplementary material). The second component primarily was composed of Word List Learning Recall and Recognition and was interpreted to reflect memory. Formulas for deriving the principal component score at the baseline examination were used to calculate the principal component scores for follow-up testing. Digit Span, mental alternations, and the COWAT were not used to calculate the principal component analysis because of the smaller number of individuals who completed these tests.