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Original Investigation

Anatomic Brain Disease in Hemodialysis Patients: A Cross-sectional Study

David A. Drew, MD,[1] Rafeeque Bhadelia, MD,[2] Hocine Tighiouart, MS,[3] Vera Novak, MD, PhD,[4] Tammy M. Scott, PhD,[5] Kristina V. Lou, MS, MPH,[1] Kamran Shaffi, MD,[1] Daniel E. Weiner, MD, MS,[1] and Mark J. Sarnak, MD, MS[1]

Background: Although dialysis patients are at high risk of stroke and have a high burden of cognitive impairment, there are few reports of anatomic brain findings in the hemodialysis population. Using magnetic resonance imaging of the brain, we compared the prevalence of brain abnormalities in hemodialysis patients with that in a control population without known kidney disease.

Study Design: Cross-sectional cohort.

Setting & Participants: 45 maintenance hemodialysis patients and 67 controls without reported kidney disease, both without history of known stroke.

Predictor: The primary predictor was dialysis status. Covariates included demographics (age, race, and sex), vascular risk factors (diabetes and hypertension), and cardiovascular disease (coronary artery disease and congestive heart failure).

Outcomes: Magnetic resonance imaging of the brain features, including severity of white matter disease and cerebral atrophy (sulcal prominence and ventricular atrophy), hippocampal size, and small-/large-vessel infarcts.

Measurements: Semiquantitative scale (0-9 for white matter disease and cerebral atrophy, 0-3 for hippocampal size) and infarct prevalence.

Results: Mean ages of hemodialysis patients and controls were 55 $\pm$ 17 (SD) and 53 $\pm$ 13 years, respectively. In comparison to controls, hemodialysis patients had more severe white matter disease (1.6 vs 0.7) and cerebral atrophy (sulcal prominence, 2.3 vs 0.6; ventricular enlargement, 2.3 vs 0.9; hippocampal size, 1.3 vs 1.0), with all $P < 0.001$. In multivariable analyses, hemodialysis status was associated independently with worse white matter disease and atrophy grades. Hemodialysis patients also had a higher prevalence of small- (17.8%) and large- (7.8%) vessel infarcts than controls (combined, 22% vs 0%; $P < 0.001$).

Limitations: The dialysis cohort likely is healthier than the overall US hemodialysis population, partly limiting generalizability.

Conclusions: Hemodialysis patients have more white matter disease and cerebral atrophy compared with controls without known kidney disease. Hemodialysis patients also have a high prevalence of unrecognized infarcts.

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INDEX WORDS: Hemodialysis; brain abnormalities; cerebral atrophy; white matter disease; magnetic resonance imaging (MRI).

Hemodialysis patients have a 2- to 6-fold higher incidence of stroke than patients in the general population.[1] This increased risk of cerebrovascular disease may reflect long-standing exposure to traditional risk factors, such as hypertension, dyslipidemia, and hyperglycemia, as well as nontraditional risk factors unique to dialysis patients, such as hemodynamic shifts associated with the hemodialysis procedure, oxidative stress, vascular calcification, and anemia.[2-4]

However, the clinical diagnosis of stroke underestimates the true burden of cerebrovascular disease in individuals in the general population.[5] Magnetic resonance imaging (MRI) of the brain is sensitive for detecting both clinical and subclinical strokes while also identifying white matter disease. Characterized by hyperintense changes seen on T2-weighted MRI, white matter disease is thought to result from ischemia and therefore is correlated highly with both vascular disease and its risk factors.[6,7] Additionally,

From the [1]Division of Nephrology, Department of Medicine, Tufts Medical Center; [2]Department of Radiology, Beth Israel Deaconess Medical Center; [3]Biostatistics Research Center, Tufts Medical Center; [4]Division of Gerontology, Beth Israel Deaconess Medical Center; and [5]Department of Psychiatry, Tufts Medical Center, Boston, MA.

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Address correspondence to Mark J. Sarnak, MD, MS, Box 391, Division of Nephrology, Tufts Medical Center, 800 Washington St, Boston, MA 02111. E-mail: msarnak@tuftsmedicalcenter.org

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MRI can provide a detailed assessment of brain volume, allowing for evaluation of atrophy and hippocampal size.[8,9] In patients without kidney disease, the presence of infarcts and white matter disease on MRI of the brain are associated with both cognitive impairment and elevated risk of future clinically apparent strokes, whereas both cerebral atrophy and smaller hippocampal volume have been associated with dementia.[10-15]

MRI data may be particularly important for categorizing future risk of stroke and helping delineate the pathogenesis of the high prevalence of cognitive impairment in hemodialysis patients.[16-20] However, there are few data for detailed findings of MRI of the brain in this population. Accordingly, we performed MRI of the brain in a cross-sectional hemodialysis cohort and compared the prevalence and severity of structural brain disease with those in controls without kidney disease. Specifically, we assessed for the presence and severity of white matter disease, cerebral atrophy, hippocampal size, and cerebral infarcts and then evaluated whether these abnormalities were more common in hemodialysis patients.

METHODS

Study Population

All patients receiving hemodialysis at 5 Dialysis Clinic Inc units and 1 hospital-based dialysis unit in the greater Boston, MA, area who enrolled at baseline in the Cognition and Dialysis Study (January 21, 2004, to June 29, 2011), a prospective cohort of maintenance hemodialysis patients, also were approached to consent for MRI of the brain. Eligibility criteria for the Cognition and Dialysis Study are described elsewhere,[20] but, briefly, required age of 18 years or older, English fluency, medically stable condition, and receipt of hemodialysis therapy for at least 1 month. The most common reasons for not undergoing MRI were lack of interest and therefore not providing consent and ineligibility for MRI due to metallic and electronic implants. Demographic information regarding history of diabetes, hypertension, coronary artery disease, stroke, and congestive heart failure was obtained through participant report, medical charts, and the Dialysis Clinic Inc and hospital databases. Patients with a history of stroke were eligible to undergo MRI of the brain but were excluded from this analysis. The Tufts Medical Center Institutional Review Board approved the study, and all dialysis participants signed informed consent.

Controls were recruited from Tufts Medical Center and Beth Israel Deaconess Medical Center, both in the Boston metropolitan area. At Tufts, controls were approached if they were already scheduled for MRI of the brain for another indication and were aged 18-75 years. For controls, the most common indications for undergoing MRI were headache (56%), vertigo (8%), and facial pain (8%). At Beth Israel Deaconess Medical Center, controls were recruited by advertisement to undergo MRI of the brain and were required to be older than 50 years.[21,22] Exclusion criteria for both centers were kidney disease, presentation with symptoms or signs of stroke or history of stroke, cerebral hemorrhage, psychiatric disease, dementia, other serious neurologic disorders, and malignancy of the brain. Self-reported demographic data for age, sex, race, and history of diabetes, hypertension, coronary artery disease, and congestive heart failure were collected. At Tufts, kidney disease was considered absent if there was documentation of estimated glomerular filtration rate (eGFR; CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] creatinine equation [2009][23]) >60 mL/min/1.73 m^2 within 1 year of MRI (80%) and through review of the medical record if eGFR was not available (20%). At Beth Israel Deaconess Medical Center, participants underwent a history and physical examination and were excluded if kidney disease was reported or suspected. All controls provided signed informed consent, which was approved by each institution's respective institutional review board.

Outcomes

MRI was performed in 45 hemodialysis patients and 67 controls. Images were obtained on a Koninklijke Philips Electronics (www.usa.philips.com) scanner, and included 3-dimensional T1-weighted coronal images, intermediate and T2-weighted conventional spin-echo axial images, and fluid attenuation inversion recovery (FLAIR) turbo spin echo axial images. White matter disease was defined as hyperintense changes on FLAIR and T2-weighted images with no corresponding T1 abnormality. A board-certified neuroradiologist (R.B.) who was blinded to clinical characteristics semiquantitatively graded white matter hyperintensity, ventricular size, sulcal prominence, and hippocampal size using previously validated criteria.[24,25] Briefly, white matter disease severity was scored on a scale of 0-9, with 0 being no detectable change and 9 being all white matter involved. Cerebral atrophy was assessed through 2 different measures: sulcal prominence (more prominence indicates more atrophy) and ventricular size (larger size indicates more atrophy). Sulcal prominence ranged from small (grade 0) to very large sulci (grade 9), whereas ventricular size ranged from slit-like (grade 0) to markedly enlarged (grade 9) ventricles. Hippocampal size was assessed on a scale of 0-3, with 0 being no atrophy and 3 being severe atrophy. Large-vessel infarcts were defined as infarcts >1.5 cm and in a major vascular territory.[26] Any infarct in a cortical location was considered to be a manifestation of large-vessel disease. Small-vessel infarcts were defined as a focal subcortical brain lesion between 3 mm and 1.5 cm, hyperintense on T2-weighted and hypointense on T1-weighted images. For a subset of both the hemodialysis cohort and control group, each outcome was rescored by the same neuroradiologist (R.B.; in a blinded manner with regard to the initial reading) to confirm the reliability of the grading system.

Statistical Analysis

Demographic characteristics for the hemodialysis and control groups were reported as mean with standard deviation or percentage and were compared using χ^2 test, Fisher exact test, t test, and analysis of variance, as appropriate. Hemodialysis patient and control data were combined and linear regression was performed to assess the association between hemodialysis status and white matter disease and cerebral atrophy in univariate analyses and after multivariable adjustment for age, sex, race, vascular disease, and vascular risk factors. For hippocampal size, the outcome was dichotomized (grades 0-1 vs 2-3) and logistic regression was performed to assess the association between dialysis status and hippocampal size, with similar multivariable adjustment for covariates. Small- and large-vessel infarcts were reported as either present or absent. All analyses were performed using SAS (version 9.2; SAS Institute Inc, www.sas.com), and all hypothesis tests were 2 sided, with $P < 0.05$ considered significant.