Changes in Cerebral Volume and White Matter Integrity in Adults on Hemodialysis and Relationship to Cognitive Function

W. T. Richerson

L. G. Umfleet

Brian D. Schmit

D. F. Wolfgram

Changes in Cerebral Volume and White Matter Integrity in Adults on Hemodialysis and Relationship to Cognitive Function

W.T. Richerson
Department of Biomedical Engineering, Marquette University and Medical College of Wisconsin, Milwaukee, WI

L.G. Umfleet
Department of Neurology, Medical College of Wisconsin, Milwaukee, WI

B.D. Schmit
Department of Biomedical Engineering, Marquette University and Medical College of Wisconsin, Milwaukee, WI

D.F. Wolfgram
Department of Medicine, Medical College of Wisconsin and Zablocki Veterans Affairs Medical Center, Milwaukee, WI, USA
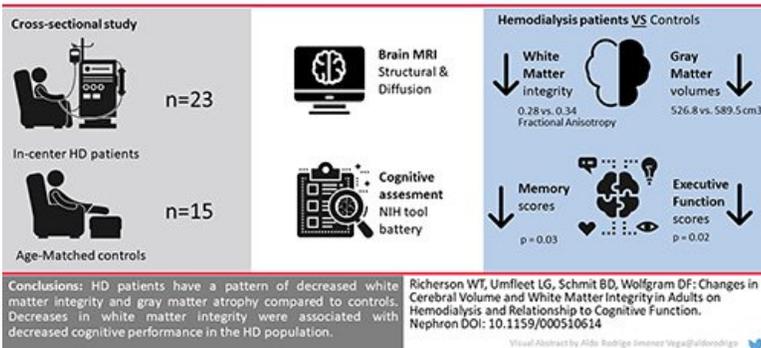
Keywords

Abstract

Changes in Cerebral Volume and White Matter Integrity in Adults on Hemodialysis and Relationship to Cognitive Function

Nephron

Cross-sectional study

In-center HD patients — n=23

Age-Matched controls — n=15

Brain MRI Structural & Diffusion

Cognitive assessment NIH tool battery

Hemodialysis patients VS Controls

White Matter integrity ↓ — 0.28 vs. 0.34 Fractional Anisotropy

Gray Matter volumes ↓ — 526.8 vs. 589.5 cm3

Memory scores ↓ — p = 0.03

Executive Function scores ↓ — p = 0.02

Conclusions: HD patients have a pattern of decreased white matter integrity and gray matter atrophy compared to controls. Decreases in white matter integrity were associated with decreased cognitive performance in the HD population.

Richerson WT, Umfleet LG, Schmit BD, Wolfgram DF: Changes in Cerebral Volume and White Matter Integrity in Adults on Hemodialysis and Relationship to Cognitive Function. Nephron DOI: 10.1159/000510614

Visual Abstract by Aldo Rodrigo Jimenez Vega @aldorodrigo

Introduction: Patients on hemodialysis (HD) have a significant burden of cognitive impairment. Characterizing the cerebral structural changes in HD patients compared to healthy controls and evaluating the relationship of cerebral structural integrity with cognitive performance in HD patients can help clarify the pathophysiology of the cognitive impairment in HD patients. ***Methods:*** In this cross-sectional study, in-center HD patients ≥50 years of age underwent brain structural and diffusion MRIs and cognitive assessment using the NIH Toolbox cognition battery. The cerebral imaging measures of the HD participants were compared to imaging from age-matched controls. Gray matter volume, white matter volume, and white matter integrity determined by diffusion tensor imaging parameters (including fractional anisotropy [FA]) were measured in both cohorts to determine differences in the cerebral structure between HD participants and healthy controls. The association between cognitive performance on the NIH Toolbox cognition battery and cerebral structural integrity was evaluated using multiple linear regression models. ***Results:*** We compared imaging measures form 23 HD participants and 15 age-matched controls. The HD participants had decreased gray matter volumes (526.8 vs. 589.5 cm^3, $p < 0.01$) and worsened white matter integrity overall (FA values of 0.2864 vs. 0.3441, $p < 0.01$) within major white matter tracts compared to healthy controls. Decreases in white matter integrity in the left superior longitudinal fasciculus was associated with lower executive function scores ($r^2 = 0.24$, $p = 0.02$) and inferior longitudinal fasciculus with lower memory scores ($r = 0.25$ and $p = 0.03$ for left and $r^2 = 0.21$ and $p = 0.03$ for right). ***Conclusions:*** HD patients have a pattern of decreased white matter integrity and gray matter atrophy compared to controls. Decreases in white matter integrity were associated with decreased cognitive performance in the HD population.

Introduction

Cognitive impairment (CI) in patients with end-stage renal disease (ESRD) treated with hemodialysis (HD) is increasingly apparent and concerning. Cohort studies demonstrate that two-thirds of HD patients suffer from CI and half of those have severe impairment that is consistent with dementia [1-4]. CI in the HD population is associated with higher mortality, increased hospitalization rates, and lower functional status and quality of life [5, 6]. In the dialysis population, CI can reduce the patients'

ability to adhere to medications and dietary restrictions that are complex and central to dialysis care. In addition, it compromises decision-making capacity regarding care. The pathophysiology of cognitive decline in this population is unclear. However, the HD population is noted to have generalized cortical atrophy and white matter disease on imaging [7-10]. This indicates that there may be cerebral structural changes that lead to the CI in this population.

Characterizing cerebral microstructural changes in HD patients can be used to identify how brain injury might be occurring and inform prevention therapies. The pathophysiology for CI is likely multifactorial with uremic toxins, inflammation, anemia, electrolyte disturbances, and proteinopathies all contributing; however, cerebral ischemia appears to play a key role. Prior evidence demonstrates an increased risk of cerebrovascular disease after initiation of HD [11]. There is evidence of white matter disease, lacunae and infarcts, and atrophy on brain imaging in HD patients [1, 8, 12, 13]. These ischemic-type lesions may be due to the circulatory stress that is induced by HD in the setting of vascular disease [14]. Cerebral hypoperfusion during HD has been demonstrated using a number of methods [15-17]. In addition to infarcts and atrophy, there may also be microstructural changes in white matter integrity that occur. These ischemic lesions, atrophy, and loss of integrity of neural pathways and structures may be the link to compromised cognitive function.

To provide further information on cerebral structural and cognitive changes in the HD population, we conducted a cross-sectional analysis using magnetic resonance imaging (MRI) and cognitive testing in an HD cohort with comparison to MRI data from healthy controls. We utilized state-of-the-art image processing methodology to improve accuracy of the measurements of white matter integrity, focusing on parameters of fractional anisotropy (FA, a measure of directional diffusion along neuronal tracts) and mean diffusivity (MD, a measure of dispersion along a tract). We hypothesized that the HD cohort would have decreased gray and white matter volumes and indicators of decreased white matter integrity compared to healthy controls. Furthermore, we hypothesized that cerebral volumes and white matter integrity would be associated with cognitive performance in the HD cohort.

Methods

Participants

In this cross-sectional analysis from an ongoing longitudinal study, we recruited participants with ESRD treated with HD from 4 community dialysis units in Milwaukee, WI. Each ESRD participant provided informed written consent to the protocol, which was approved by the Institutional Review Board at the Medical College of Wisconsin. Inclusion criteria were age ≥50 years and receiving thrice weekly conventional in-center HD. Participants also had to be on dialysis over 1 month but <2 years at enrollment. The 1 month was to avoid the complicating effects of untreated uremia, and the <2-year requirement was to capture when cognitive changes may be more commonly occurring as part of the longitudinal study. Exclusion criteria included a history of stroke, traumatic brain injury, brain tumor or surgery within the past year, non-English speaking, hearing or vision impairment enough to preclude the ability to take the cognitive tests, severe CI that would prevent them from completing cognitive testing, or diagnosis of dementia. Healthy control data were used from a previous study [18]. The healthy control group had the same imaging protocol as the HD cohort but did not have the cognitive

testing. Both the HD and control groups' imaging were processed and analyzed using the same processing pipeline described below.

Cognitive Testing

Each HD participant completed the NIH Toolbox cognition battery, which includes 7 assessments that evaluate the following domains: language, attention, processing speed, executive function, working memory, and episodic memory, as well as 3 composite scores [19]. Testing was performed the day after the participant's 2nd dialysis session of the week. This was to avoid the immediate changes in cognition during and immediately after a dialysis session [20]. All testing was carried out in a quiet room with a test administrator and completed on an iPad.

Magnetic Resonance Imaging

MRI was performed on the same day as the cognitive testing, immediately following the cognitive testing. No participant was given anti-anxiety or sedative medications for the scan. Every participant completed an MRI safety screen prior to the scan. T1-weighted anatomical images were acquired using an axial fast spoiled gradient recall 3D sequence (TE = 3.2 ms, TR = 8.16 ms, flip angle = 12°, prep time = 450, bandwidth = 22.73, FOV = 240 mm, 156 1-mm slices, and matrix = 256 × 240). The diffusion-weighted volumes were acquired using an axial q-ball high angular resolution diffusion imaging sequence using single-shot echo-planar imaging (TE = 72.3 ms, TR = 5,700 ms, b-value = 1,500 s/mm^2, 5 b0 images, 150 directions, FOV = 256 mm, 59 2.5-mm slices, and matrix = 128 × 128).

Image Processing

Anatomical morphometry processing, including bias correction, skull stripping, spatial normalization, and segmentation, was completed using cat12 (http://www.neuro.uni-jena.de/cat/). Total volumes of gray matter, white matter, and cerebrospinal fluid and total intracranial volume were calculated with segmented anatomical volumes. Region of interest analysis was carried out by masking the gray matter segmentation of each participant with the Harvard-Oxford Cortical and Subcortical Atlases and the Probabilistic Cerebellar Atlas [21, 22]. For the diffusion processing, diffusion volumes were skull stripped and corrected for susceptibility in the images, interslice and intraslice and volume motion, signal dropout, and b-vector correction [23, 24]. Diffusion volumes were registered using a rigid transform from diffusion to anatomical space, and a combination of affine and nonlinear registration was used to obtain the transforms from anatomical to standard MNI 152 Nonlinear 1-mm space.

After completing registration, the tensor model was then fit to each voxel in the diffusion volume to get the diffusion tensor imaging (DTI) measures of microstructural integrity (FA, axial diffusion [AD], radial diffusion [RD], and MD). FA is a measure of the strength of diffusion in the primary direction relative to the nonprimary diffusion directions, MD is the average diffusivity in a certain voxel, AD is the magnitude of diffusion in the primary direction, and RD is the average of the diffusivity in the 2 nonprimary diffusion directions. FA is correlated positively with general white matter integrity. MD is negatively correlated with white matter integrity as more diffusion in all directions would mean less white matter tracts to restrict diffusion. An increase in RD may indicate demyelination as the nonprimary diffusion directions are perpendicular to the white matter tracts, and any increased diffusion in these directions is a marker of decreased restriction of diffusion in these directions. AD has been previously correlated with axon density as it measures the diffusion along the white matter

tracts; a decrease indicates a loss of white matter organization to channel diffusion in the direction of the white matter tract [25-28].

Identifying Tract Regions of Interest

White matter tract regions of interest (tROIs) were delineated for calculating diffusion parameters for specific tracts. FSL's probabilistic tractography function probtrackx was used to generate white matter tracts [29]. Seed, termination, and exclusion masks for 27 white matter tracts were used [30]. For each tract, 5,000 streamlines were run per voxel seeded and the resulting tract density images were thresholded at 0.2 to remove noisy tracts from the ROIs. The ROIs were then warped to anatomical space where non-white matter regions identified by using the FSL's fast segmentation algorithm of the anatomical data were removed from the tROIs for each participant, resulting in 27 tROIs encompassing only white matter. Each measure of white matter microstructural integrity (FA, AD, RD, and MD) was then averaged within each tROI and used for statistical analyses.

Analysis

Cognitive Performance Analysis

Tests were scored automatically in the NIH Toolbox app. The HD cohort scores were compared to age-corrected standard population means of 100 with an SD of 15 using one-sided t tests with a CI of 95%.

Anatomical Statistical Analysis

Total gray matter, white matter, and cerebrospinal fluid were compared between the HD and control groups, controlling for total intracranial volume and age effects, using FSL's PALM software in MATLAB. This comparison was repeated for each gray matter ROI identified using the Harvard-Oxford and Probabilistic Cerebellar Fusion Atlas [21, 22, 31-33] to identify cortical regions in which the volume was significantly smaller in the HD cohort compared to controls. False discovery rate was used to correct for multiple comparisons.

Diffusion Statistical Analysis

Whole brain white matter DTI measures were compared between the 2 groups using an ANCOVA with age as a confounding variable. In addition, an ANCOVA analysis was conducted for each tROI identified with tractography using false discovery rate to correct for multiple comparisons (corrected $p < 0.05$). Whole brain white matter and tROI results were then used in multiple linear regression models with age and white matter microstructural integrity as 2 predictors and cognitive scores as the response variable; models were made for each tract and cognitive task. Although we evaluated 27 white matter tracts and 10 cognitive scores, we did not perform multiple comparisons on this specific analysis given the initial small dataset and preliminary nature of this component of the study.

Results

We had 190 HD patients met age and <2 years on HD criteria, but of those, 123 were excluded due to exclusion criteria or too sick to complete study procedures. Out of the remaining 67 eligible participants, 32 consented to participate. Subsequently 3 changed their mind due to having to go off-site for MRI, 5 were unable to get MRI due to MRI screening failure or claustrophobia, and 1 image was not used due to large strokes that led to DTI parameters and volumes that were statistically noted as

outliers. We included 23 HD participants and 15 healthy controls in the analysis. The mean age of the HD cohort was 66.3 versus 62.3 in healthy controls, p = 0.11 (see Table 1). Demographics including age, race, and gender as well as HD duration and medical comorbidities are noted in Table 1.

Table 1. Age and gender differences between HD participants and healthy controls and HD comorbidities

	Group		
	HD participants ($n = 23$)	healthy controls ($n = 15$)	p value
Age (SD)	66.3	62.3	0.11
Male, %	65.2	53.3	0.13
Hemodialysis duration, months	7.8±6.7	N/A	−
Comorbidities, n (%)			
Hypertension	18 (78.3)	N/A	−
Diabetes	15 (65.2)		
CAD	9 (39.1)		
PVD	3 (13.0)		
CHF	9 (39.1)		
Race, n (%)			
Caucasian	14 (60.9)		
African American	7 (30.4)		
Others	2 (8.7)		
Cause of ESRD, n (%)			
Diabetes	11 (47.8)	N/A	−
Hypertension	6 (26.1)		
Others	6 (26.1)		
Educational level, n (%)			
High school or less	13 (56.5)		
Some college/bachelor's degree	8 (34.8)		
Advanced degree	2 (8.7)		

HD, hemodialysis; CAD, coronary artery disease; PVD, peripheral vascular disease; CHF, congestive heart failure; ESRD, end-stage renal disease. Advanced degree indicates masters', graduate, or professional degree.

Cerebral Volumes in HD Cohort Compared to Controls

Global gray matter volume adjusted for age and total intracranial volume was lower in the HD cohort than in healthy controls (526.8 vs. 589.5 cm^3, p < 0.01) (Fig. 1). Regionally, the left putamen, bilateral pallidum, bilateral VIIa cerebellar lobules, and right VIIb cerebellar lobule were significantly decreased in HD patients after multiple comparisons correction (Fig. 2). There were no regions with higher gray matter volumes in HD patients compared to controls. Cerebrospinal fluid volume was significantly greater in HD patients (415.4 vs. 335.5 cm^3, p < 0.01), while white matter volume was not significantly different between the 2 groups (470.8 vs. 490.4 cm^3, p = 0.20), shown in Figure 1.

Fig. 1. Total GM, WM, and CSF volumes after controlling for age and total intracranial volume as confounding variables. Significance labels represent significance p < 0.01**. There is a decrease in GM and WM volume along with increase in CSF volume in the hemodialysis cohort compared to healthy control indicating generalized atrophy. GM, gray matter; WM, white matter; CSF, cerebral spinal fluid; HD, hemodialysis.

Volume comparison (corrected for total intracranial volume)
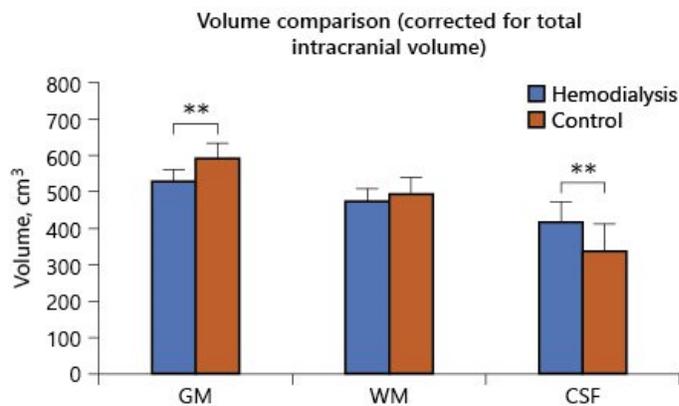
Fig. 2. T map of significant ($p < 0.05$) volume differences in individual ROIs derived from the Harvard-Oxford Cortical and Subcortical Atlases and Probabilistic Cerebellar Atlas. Cortical and subcortical atlases are shown on the right and cerebral atlas on the left. The color graph on the right indicates the difference in volume in cm^3 with yellow indicating a larger difference. The highlighted subcortical structures include the left putamen and bilateral pallidum. ROIs, regions of interest.
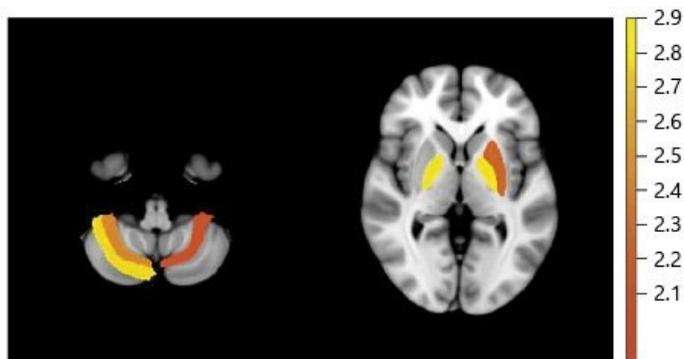
White Matter Microstructural Integrity in HD Cohort Compared to Controls

Global white matter FA was significantly lower in HD patients compared to controls (0.2864 vs. 0.3441, $p < 0.01$), shown in Figure 3, with significantly higher mean AD (0.001 vs. 0.00097, $p < 0.01$), RD (6.47×10^{-4} vs. 5.60×10^{-4}, $p < 0.01$), and MD (7.65×10^{-4} vs. 6.97×10^{-4}, $p < 0.01$) values. The lower FA in HD patients compared to controls was present in 17 out of the 27 tracts measured (see FA bar plot in online suppl. Fig. 1; see www.karger.com/doi/10.1159/000510614 for all online suppl. material,). The absolute differences in FA for all significantly different white matter tracts are shown in Figure 3. In addition, most of the decreased tracts had increased RD (see RD bar plot in online suppl. Fig. 1).

Fig. 3. Map of significant FA differences in tracts identified using tractography and whole white matter difference in FA between the groups. On the left are the FA differences in tracts using tractography, and tROIs were summed and mapped as the FA difference between the 2 groups. Highlighted tracts all have statistically significant differences compared to controls with $p < 0.01$. The degree of differences in FA is shown with the color graph, with yellow indicating a higher difference. On the right is the difference in whole white matter FA between the groups, with $p < 0.01$. HD, hemodialysis; FA, fractional anisotropy; tROIs, tract regions of interest.
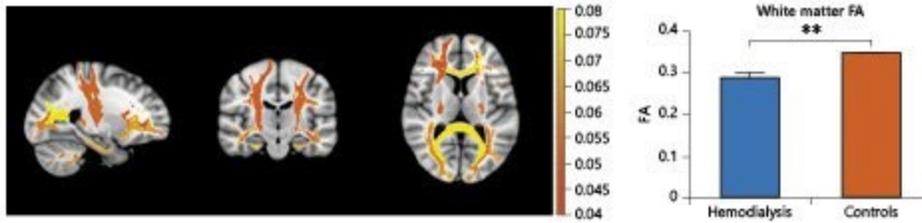
Cognitive Performance in HD Cohort

NIH Toolbox Cognitive Function scores for the HD cohort are displayed in Table 2, with p values for comparisons with age-corrected standard population scores (mean = 100 and SD = 15 for all scores). The mean (SD) total cognition composite score in the HD cohort was 92.4 (15.2), significantly less (p = 0.02) than the age-corrected population scores. This difference was primarily due to differences in fluid measures. The Fluid Cognition Composite (86.9 [14.3]) and its components of pattern comparison processing speed (83.1 [16.1]) and flanker inhibitory executive function and attention test (84.3 [10.1]) were all significantly less than population scores. The Crystallized Cognition Composite Score (99.1 [14.5]) and all components of it were similar to population scores.
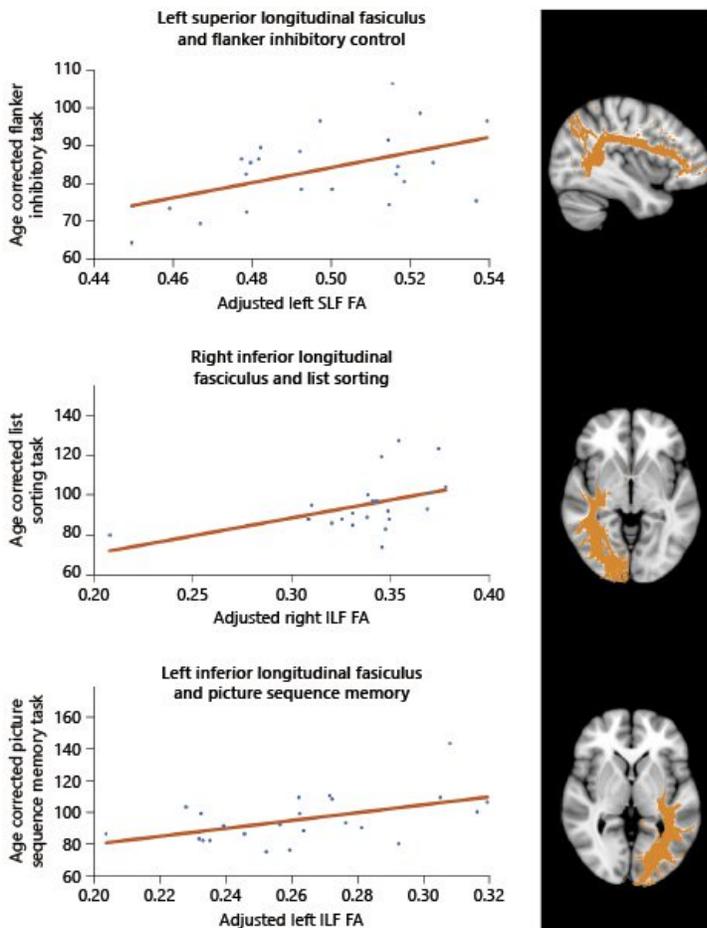
Table 2. HD cohort scores on NIH Toolbox tasks with cognitive domain for each test

Cognitive tests	Cognitive domain	Score, mean (SD)	p value
Picture vocabulary	Language	97.7 (12.6)	0.20
Oral reading	Language	99.9 (15.0)	0.49
Crystallized cognition composite[a]	N/A	99.1 (14.5)	0.39
Flanker inhibitory control and attention	**Executive function and attention**	**84.3 (10.1)**	**<0.01**
List sorting	Working memory	96.3 (12.4)	0.09
Dimensional change card sort	Executive function	96.7 (15.0)	0.15
Pattern comparison processing speed	**Processing speed**	**83.1 (16.1)**	**<0.01**
Picture sequence memory	Episodic memory	95.4 (15.0)	0.08
Fluid cognition compositea	**N/A**	**86.9 (14.3)**	**<0.01**
Total cognition composite	**N/A**	**92.4 (15.2)**	**0.02**

Cognitive Function and Cerebral Imaging Parameters in HD Cohort

There were no associations between total gray white or total white matter and cognitive scores in the HD cohort. In evaluating the tROI FA values and cognitive function, there was a small, but statistically significant, positive relationship between microstructural integrity of the left superior longitudinal fasciculus and scores on the test of executive function and attention (r^2 = 0.24, p = 0.02) and left inferior longitudinal fasciculus (r^2 = 0.25 and p = 0.03) and right inferior longitudinal (r^2 = 0.21 and p = 0.03) with tests of memory, as shown in Figure 4.

Fig. 4. Graph of white matter tract FA values with scores on cognitive tasks. The top panel shows the relationship between the left SLF FA values and the age-corrected score of the flanker inhibitory test, which measures both executive function and attention. The middle and bottom panels show the relation between the right and left ILF FA values and tests of working (list sorting) and episodic memory (picture sequence), respectively. The FA values are adjusted for age, and a higher FA indicates better white matter integrity. The cortical images on the right outline the respective tracts. FA, fractional anisotropy; SLF, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus.

Left superior longitudinal fasiculus and flanker inhibitory control

Right inferior longitudinal fasciculus and list sorting

Left inferior longitudinal fasiculus and picture sequence memory

Discussion

We found evidence of cerebral degeneration with lower gray matter volume, higher cerebrospinal fluid volumes, and decreased microstructural integrity of most major white matter tracts (noted by lower FA values and higher MD values) in HD patients relative to healthy age-matched controls. The greatest decreases in white matter integrity were observed in areas of the brain used in executive function and processing speed, cognitive domains in which our HD cohort performed worse than age-adjusted standard population scores. Finally, we found that lower white matter integrity in specific white matter tracts was associated with decreased cognitive performance in our HD patients. Previous studies have found cerebral structural changes; however, we identified that these changes are present early after dialysis initiation and found new subcortical changes that have not been previously noted. The cerebral structural changes we note and the association with cognitive performance support our framework of an HD-associated cerebral injury that has an impact on cognitive function.

While prior studies of persons with ESRD have documented lower brain matter volumes and global decreases in white matter integrity relative to controls [7, 10, 34], our study adds information on specific DTI parameters and examines these changes in white matter integrity within specific tracts. In our analysis, 17 of 27 measured tracts had decreased FA in HD patients relative to controls. Many of the tracts affected, including the forceps minor, cingulum, and uncinate fasciculus, project to the frontal cortex and therefore have important roles in cognition and executive function. We also found

that in most tracts, the decreased tract FA was due to an increase in the RD measurements, which may indicate more demyelination of white matter [26, 28]. These results indicate that there is disruption in the majority of white matter tracts in the HD cohort, with decreased overall white matter integrity, characterized by decreased FA.

An important strength of our approach was to preidentify the major white matter tracts of the brain. Previous studies have used voxel-wise tract-based spatial statistics [10, 34] to characterize changes in white matter integrity. Those methods restrict the area of white matter that is used for quantification to the highest FA regions (rather than the whole tract), which reduces complications of identifying tract boundaries, but is susceptible to systemic misalignment issues [35, 36]. Tract-based spatial statistics also requires post hoc assignment of white matter regions to specific tracts. Another method used manual segmentation of white matter into regions based on the cortical location (frontal, parietal, etc.) [7], which depends on subjective criteria for tract identification. With our unique processing method, we incorporated individual variation in white matter tract architecture by identifying white matter tract regions using tractography, avoiding potential misalignment issues that can occur in other approaches. The accuracy of this method is demonstrated by the fact that we found differences in white matter integrity despite no difference in white matter volume.

In addition to white matter changes, we found evidence of gray matter atrophy, with lower gray matter volume and higher cerebrospinal fluid volumes in the HD cohort. We found primarily subcortical (putamen and pallidum) and cerebellar gray matter volume differences. This differs from prior studies that found mostly cortical volume changes [9, 37] and provides new information on brain structural changes and CI in HD patients. The lack of significant cortical volume decreases in our study compared to prior studies may also be due to differences in our study demographics. The populations included in prior studies were 30 years younger on average and had minimal or no CI compared to our cohort [9, 37]. Our cohort is more reflective of the current HD population in both age and CI [38]. Cohort age is important since cortical gray matter volume decreases with age [39, 40]. The known age-related decreases in cortical gray matter volume might have reduced the differences in cortical gray matter between the HD participants and controls in our older cohort. Alternatively, our cohort had a lower dialysis vintage compared to prior study cohorts and we may be detecting initial changes that occur before the cortical gray matter changes. The differences in subcortical gray matter that we observed raise the possibility that changes in subcortical gray matter volume might play a role in CI in older HD patients. The decrease in putamen gray matter volume in the HD cohort may be important as lesions in the putamen have been associated with impairments in memory and processing speed in other neurological disease states and aging [41, 42].

To examine the potential effects of the cerebral structural changes, we evaluated the relationship between cognitive performance and brain imaging parameters. The pattern of NIH Toolbox scores we noted in our cohort – greatest performance differences in processing speed, executive function, and attention domains and less but still notable differences in memory – is consistent with prior literature [43-46]. The relationships between the superior longitudinal fasciculus FA and performance on executive function and attention tasks and between the inferior longitudinal fasciculus FA and memory tasks are also consistent with other studies [47, 48]. A study evaluating white matter integrity in 26 HD patients found a similar correlation of lower white matter integrity in superior longitudinal fasciculi

with lower performance on executive function and processing speed [34]. Although we did not correct for multiple comparison in our small sample, the trends in our results support the general theory that decreased white matter integrity is associated with worse cognitive performance. Many of the white matter tracts in the HD patients had decreased FA values compared to controls, including the inferior fronto-occipital fasciculus, forceps major, and uncinate fasciculus; all of which project to the frontal cortex, a structure important in executive function, an area of deficit in HD patients [49].

Our study has limitations. Our small sample size may have reduced our ability to identify statistically significant associations between the integrity of specific white matter tracts and cognitive performance. Our controls were healthy volunteers and thus were not matched in rates of comorbidities such as diabetes and hypertension. We cannot determine if the changes in brain matter are due to comorbidities, renal disease, or HD. However, this does not limit our ability to describe the brain changes in HD patients versus healthy controls and to evaluate the relationship between cognitive score and cerebral imaging parameters in HD patients. We relied on comparison to age-adjusted population norms to identify the cognitive deficits in the HD cohort. However, using general population norms allowed us to compare our HD cohort to a larger sample rather than just our 15 controls. In terms of imaging processing, the tensor model we used is limited in regions with crossing tracts [50]. We believe the methodology performed better than generic group-defined tract masks by accurately identifying specific tracts in individual participants. We noted misalignment, with tracts going through gray matter or CSF when using generic masks, which were not present when using our tractography method. Finally, our cross-sectional study design only allowed us to look for associations between variables at 1 point in time. An ongoing longitudinal study will provide further information on how HD may affect the brain over time.

In summary, we found that HD patients had lower white matter integrity and more gray matter atrophy than controls. The changes in white matter integrity in certain tracts were associated with decreased cognitive performance noted in the HD group. Future studies need to replicate our methods in a larger cohort to confirm findings. In addition, longitudinal studies evaluating changes in the integrity of white matter tracts over time in HD participants are needed to determine if HD-specific factors contribute to white matter changes. Increased focus in this area of research is needed in order to better understand and prevent the CI and neurodegeneration in HD patients.

Statement of Ethics

This study conformed to the standards set by the latest revision of the Declaration of Helsinki and was approved by the Institutional Review Board of the Medical College of Wisconsin. Written informed consent was obtained for each subject in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Author Contributions

References

1. Fazekas G, Fazekas F, Schmidt R, Kapeller P, Offenbacher H, Krejs GJ. Brain MRI findings and cognitive impairment in patients undergoing chronic hemodialysis treatment. J Neurol Sci. 1995 Dec;134(1–2):83–8.
2. Pereira AA, Weiner DE, Scott T, Sarnak MJ. Cognitive function in dialysis patients. Am J Kidney Dis. 2005 Mar;45(3):448–62.
3. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, et al. Cognitive impairment in hemodialysis patients is common. Neurology. 2006 Jul 25;67(2):216–23.
4. Wolfgram D, Vogt E, Jahn AL, Smith HM, Sussman J, Visotcky A, et al. Hemodynamics during dialysis and changes in cognitive performance. WMJ. 2014 Aug 8;115(6):311.
5. Kimmel PL, Thamer M, Richard CM, Ray NF. Psychiatric illness in patients with end-stage renal disease. Am J Med. 1998 Sep;105(3):214–21.
6. Kurella M, Mapes DL, Port FK, Chertow GM. Correlates and outcomes of dementia among dialysis patients: the dialysis outcomes and practice patterns study. Nephrol Dial Transplant. 2006 Sep;21(9):2543–8.
7. Hsieh TJ, Chang JM, Chuang HY, Ko CH, Hsieh ML, Liu GC, et al. End-stage renal disease: in vivo diffusion-tensor imaging of silent white matter damage. Radiology. 2009 Aug;252(2):518–25.
8. Drew DA, Bhadelia R, Tighiouart H, Novak V, Scott TM, Lou KV, et al. Anatomic brain disease in hemodialysis patients: a cross-sectional study. Am J Kidney Dis. 2013 Feb;61(2):271–8.
9. Zhang LJ, Wen J, Ni L, Zhong J, Liang X, Zheng G, et al. Predominant gray matter volume loss in patients with end-stage renal disease: a voxel-based morphometry study. Metab Brain Dis. 2013 Dec;28(4):647–54.
10. Kong X, Wen JQ, Qi RF, Luo S, Zhong JH, Chen HJ, et al. Diffuse interstitial brain edema in patients with end-stage renal disease undergoing hemodialysis: a tract-based spatial statistics study. Medicine. 2014 Dec;93(28):e313.
11. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. J Am Soc Nephrol. 2013 Jun;24(7):1166–73.
12. Yoshimitsu T, Hirakata H, Fujii K, Kanai H, Hirakata E, Higashi H, et al. Cerebral ischemia as a causative mechanism for rapid progression of brain atrophy in chronic hemodialysis patients. Clin Nephrol. 2000 Jun;53(6):445–51.
13. Seliger SL, Weiner DE. Cognitive impairment in dialysis patients: focus on the blood vessels? Am J Kidney Dis. 2013 Feb;61(2):187–90.
14. McIntyre CW. Recurrent circulatory stress: the dark side of dialysis. Semin Dial. 2010 Sep–Oct;23(5):449–51.

15. MacEwen C, Sutherland S, Daly J, Pugh C, Tarassenko L. Relationship between hypotension and cerebral ischemia during hemodialysis. J Am Soc Nephrol. 2017 Aug;28(8):2511–20.

16. Polinder-Bos HA, García DV, Kuipers J, Elting JWJ, Aries MJH, Krijnen WP, et al. Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. J Am Soc Nephrol. 2018 Apr;29(4):1317–25.

17. Findlay MD, Dawson J, Dickie DA, Forbes KP, McGlynn D, Quinn T, et al. Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. J Am Soc Nephrol. 2019 Jan;30(1):147–58.

18. Kalinosky BT, Schindler-Ivens S, Schmit BD. White matter structural connectivity is associated with sensorimotor function in stroke survivors. Neuroimage Clin. 2013;2:767–81.

19. Heaton RK, Akshoomoff N, Tulsky D, Mungas D, Weintraub S, Dikmen S, et al. Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in adults. J Int Neuropsychol Soc. 2014 Jul;20(6):588–98.

20. Murray AM, Pederson SL, Tupper DE, Hochhalter AK, Miller WA, Li Q, et al. Acute variation in cognitive function in hemodialysis patients: a cohort study with repeated measures. Am J Kidney Dis. 2007 Aug;50(2):270–8.

21. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006 Jul 1;31(3):968–80.

22. Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N. A probabilistic MR atlas of the human cerebellum. Neuroimage. 2009 May 15;46(1):39–46.

23. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. Magn Reson Med. 2009 Jun;61(6):1336–49.

24. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage. 2016 Jan 15;125:1063–78.

25. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J. 1994 Jan;66(1):259–67.

26. Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage. 2003 Nov;20(3):1714–22.

27. Hagmann P, Jonasson L, Maeder P, Thiran JP, Wedeen VJ, Meuli R. Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. Radiographics. 2006 Oct;26(Suppl 1):S205–23.

28. Winklewski PJ, Sabisz A, Naumczyk P, Jodzio K, Szurowska E, Szarmach A. Understanding the physiopathology behind axial and radial diffusivity changes-what do we know? Front Neurol. 2018;9:92.

29. Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med. 2003 Nov;50(5):1077–88.

30. de Groot M, Vernooij MW, Klein S, Ikram MA, Vos FM, Smith SM, et al. Improving alignment in tract-based spatial statistics: evaluation and optimization of image registration. Neuroimage. 2013 Aug 1;76:400–11.

31. Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, et al. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry. 2005 Jul;162(7):1256–65.

32. Makris N, Goldstein JM, Kennedy D, Hodge SM, Caviness VS, Faraone SV, et al. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr Res. 2006 Apr;83(2–3):155–71.

33. Goldstein JM, Seidman LJ, Makris N, Ahern T, O'Brien LM, Caviness VS Jr, et al. Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. Biol Psychiatry. 2007 Apr 15;61(8):935–45.

34. Zhang R, Liu K, Yang L, Zhou T, Qian S, Li B, et al. Reduced white matter integrity and cognitive deficits in maintenance hemodialysis ESRD patients: a diffusion-tensor study. Eur Radiol. 2015 Mar;25(3):661–8.

35. Zalesky A. Moderating registration misalignment in voxelwise comparisons of DTI data: a performance evaluation of skeleton projection. Magn Reson Imaging. 2011 Jan;29(1):111–25.

36. Bach M, Laun FB, Leemans A, Tax CM, Biessels GJ, Stieltjes B, et al. Methodological considerations on tract-based spatial statistics (TBSS). Neuroimage. 2014 Oct 15;100:358–69.

37. Qiu Y, Lv X, Su H, Jiang G, Li C, Tian J. Structural and functional brain alterations in end stage renal disease patients on routine hemodialysis: a voxel-based morphometry and resting state functional connectivity study. PLoS One. 2014;9(5):e98346.

38. Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D, et al. US renal data system 2019 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2020;75(1 Suppl 1):A6–7.

39. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci. 2003 Mar;6(3):309–15.

40. Farokhian F, Yang C, Beheshti I, Matsuda H, Wu S. Age-related gray and white matter changes in normal adult brains. Aging Dis. 2017 Dec;8(6):899–909.

41. Bäckman L, Ginovart N, Dixon RA, Wahlin TB, Wahlin A, Halldin C, et al. Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am J Psychiatry. 2000 Apr;157(4):635–7.

42. Mak E, Bergsland N, Dwyer MG, Zivadinov R, Kandiah N. Subcortical atrophy is associated with cognitive impairment in mild Parkinson disease: a combined investigation of volumetric changes, cortical thickness, and vertex-based shape analysis. AJNR Am J Neuroradiol. 2014 Dec;35(12):2257–64.

43. Weiner DE, Scott TM, Giang LM, Agganis BT, Sorensen EP, Tighiouart H, et al. Cardiovascular disease and cognitive function in maintenance hemodialysis patients. Am J Kidney Dis. 2011 Nov;58(5):773–81.

44. Sarnak MJ, Tighiouart H, Scott TM, Lou KV, Sorensen EP, Giang LM, et al. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. Neurology. 2013 Jan 29;80(5):471–80.

45. O'Lone E, Connors M, Masson P, Wu S, Kelly PJ, Gillespie D, et al. Cognition in people with end-stage kidney disease treated with hemodialysis: a systematic review and meta-analysis. Am J Kidney Dis. 2016 Jun;67(6):925–35.

46. Kurella Tamura M, Vittinghoff E, Hsu CY, Tam K, Seliger SL, Sozio S, et al. Loss of executive function after dialysis initiation in adults with chronic kidney disease. Kidney Int. 2017 Apr;91(4):948–53.

47. Biesbroek JM, Kuijf HJ, van der Graaf Y, Vincken KL, Postma A, Mali WP, et al. Association between subcortical vascular lesion location and cognition: a voxel-based and tract-based lesion-symptom mapping study. The SMART-MR study. PLoS One. 2013;8(4):e60541.

48. Herbet G, Zemmoura I, Duffau H. Functional anatomy of the inferior longitudinal fasciculus: from historical reports to current hypotheses. Front Neuroanat. 2018;12:77.

49. Robinson H, Calamia M, Gläscher J, Bruss J, Tranel D. Neuroanatomical correlates of executive functions: a neuropsychological approach using the EXAMINER battery. J Int Neuropsychol Soc. 2014 Jan;20(1):52–63.

50. Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? Neuroimage. 2007 Jan 1;34(1):144–55.