Neurocognitive Dysfunction in Chornic Kidney Disease (CKD) patients - correlations with DTI

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INTRODUCTION: Chronic kidney disease (CKD) affects nearly 10 million adults in the US, and these individuals suffer from diminished functional capacity, worse cognitive function[1], and a greater risk of dementia[2] relative to individuals without renal disease. The purpose of this study is to determine whether alterations in the brain white matter accounts for lower neurocognitive function in CKD patients. We examined cerebral changes in 41 older adults with stage 3-4 CKD using whole brain and regional analysis as well as voxel-based morphometry of diffusion tensor imaging (DTI) in correlation with their neurocognitive performance.

METHODS: 41 stroke-free, dementia-free older adults with stage 3-4 CKD (age: 71.5±8.4, estimated glomerular filtration rate (eGFR) 36.4±9.6 cc/min) were enrolled. Neurocognitive assessment included tests of psychomotor speed (Grooved pegboard tests, Trail-Making test part A), verbal and non-verbal memory (Visual recall, logical memory), visuospatial function (Judgment of Line Orientation), attention/concentration (Digit span tests,), mental flexibility/executive function (Stroop color-word interference test, Symbol-digit substitution test), and category fluency.

Imaging: All CKD patients were imaged with conventional MRI and DTI. Diffusion tensor images were obtained in 12 directions at an effective b-value of 1000 s/mm^2. All imaging was performed on a 1.5T Siemens Avanto scanner using a 12 channel head-neck coil. Other imaging parameters were: FOV 23cm^2; matrix 128x128; slice thickness 2mm with no gap; 3 averages; and a TE/TR of 95/11200ms, parallel imaging (GRAPPA) with a reduction factor of 2 was used. A total of 68 axial images were acquired to cover from top of the brain to the skull base.

Data Analysis: DTI images were exported offline and processed using FDT (FMRIB Diffusion Toolbox, Analysis Group, FMRIB, Oxford, UK). *Whole brain white matter (WM) histogram:* For whole brain analysis, the FA maps of all patients and controls were segmented into gray matter, white matter, and CSF categories using SPM5 (Wellcome Department of Imaging Sciences; University College London, UK). The segmented white matter masks were then used to generate whole brain white matter ADC and FA histograms. *Voxel-based analysis:* FA map from each individual patient was spatially normalized to a MNI space FA template using the non-linear normalization module in SPM5. Multi-linear regression was then performed at a voxel level, adjusting for age, gender, and race. *ROI measures:* FA and ADC values were also measured in ROIs within the following regions: temporal lobe (TL), thalamus, frontal white matter at later ventricle body level (FL), centrum semiovale (CS), internal capsule (IC) and corpus callosum (CC) at genu, splenium and body.

RESULTS: Among CKD patients, both whole brain white matter FA and ADC mean value were strongly correlated with Grooved pegboard test (r = -0.36 for FA and r=0.53 for ADC, p<.03) and Symbol-digit substitution test (r=0.36 for FA and r=-0.37 for ADC p<.03). Although there was a trend for mean FA to correlate with Trail-making test and digital span test, this trend was not significant (p<0.07). Similarly ADC exhibited a trend with the Trail-making tests and visual recall immediate test but was not significant (p<0.1 & p<0.7 respectively. Table 1 shows the correlation coefficients between FA/ADC values for the various regions and the neurocognitive scores (only tests that yield a significant correlation are included in the table). Figure 1 shows two representative voxel-based p-value maps of significantly correlated FA/ADC with Grooved pegboard test (Figure 1(a)) and Visual recall-immediate (Figure 1(b)). All significant correlations were in the direction of more disrupted white matter (greater ADC, lower FA) with declining neurocognitive function.

Regions	TL		Thamalus		FL		CC-Genu		CC-Splenium		CC-body		CS		IC	
Tests	ADC	FA	ADC	FA	ADC	FA	ADC	FA	ADC	FA	ADC	FA	ADC	FA	ADC	FA
Tr A	0.08	-0.20	0.00	-0.01	0.22	-0.25	0.33	-0.36	0.05	-0.18	0.01	0.01	0.12	-0.27	-0.04	-0.22
Tr B	0.19	-0.24	0.16	-0.11	0.30	-0.33	0.25	-0.18	0.12	-0.04	0.28	-0.05	0.32	-0.34	0.17	-0.16
Gp-d	0.40	-0.19	0.44	-0.50	0.64	-0.50	0.67	-0.53	0.46	-0.26	0.35	-0.20	0.61	-0.43	0.38	-0.06
Gp-ND	0.37	-0.47	0.06	-0.47	0.39	-0.47	0.48	-0.48	0.19	-0.29	0.04	-0.04	0.33	-0.29	0.13	-0.15
VR-Imm	-0.35	0.20	-0.07	0.33	-0.43	0.33	-0.44	0.39	-0.17	0.14	-0.25	0.11	-0.30	0.34	-0.09	0.16
VR-Del	-0.20	0.21	0.03	0.25	-0.22	0.25	-0.27	0.21	-0.10	-0.01	-0.38	0.19	-0.09	0.29	0.07	-0.15
Stroop	-0.14	0.27	-0.17	0.25	-0.26	0.25	-0.13	0.14	-0.09	-0.01	-0.29	0.09	-0.35	0.39	-0.12	0.23
Sdmt_cor	-0.29	0.37	-0.36	0.32	-0.33	0.32	-0.23	0.12	-0.24	0.08	-0.34	0.07	-0.41	0.42	-0.35	0.23
Cat_fluency	-0.30	0.20	-0.10	0.45	-0.29	0.45	-0.32	0.27	-0.17	-0.05	-0.23	-0.05	-0.12	0.22	-0.22	-0.10

Table 1. Correlation coefficients of FA/ADC values of various brain regions with cognitive scores, corrected for age, gender, race. Correlation coefficients in red are with $p < 0.05$ and blue are with $p < 0.1$. Tr A: Trail-making part A, Tr B: Trails part B, Gp -D: Grooved Pegboard, dominant hand, Gp- ND: Grooved Pegboard, non-dominant hand, VR - Imm: Visual recall, immediate, VR-Del: Visual recall, delayed, Stroop: Stroop color-word interference test, Sdmt_cor: Symbol-digit substitution test, Cat_fluency: Category fluency test.

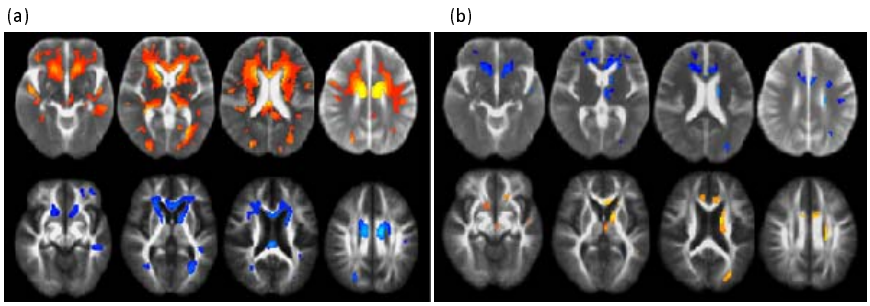

Figure 1. P-value maps (p<0.05 corrected) of significantly correlated ADC (upper row) and FA (lower row) values with Grooved pegboard, dominant hand (a) and Visual recall, immediate (b) tests. Red shows positive correlation and blue shows negative correlation.

CONCLUSION: In this study, we observed lower FA and higher ADC (indicating white matter disruption) that correlated with poor performance on various cognitive tests. An alteration to white matter structure - possibly due to generalized microvascular disease - may in part explain the observed pattern of cognitive decline.

REFERENCES: [1] Seliger SL et al. *J Am Soc Nephrol* 2004; 15:1904-11. [2] Kurella M et al. *J Am Geriatr Soc*, 2004; 52:1863-9.