Diffusion Alterations in White Matter Brain Regions in HIV Patients

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Purpose: Patients infected with Human Immunodeficiency Virus (HIV) are vulnerable to brain injury and cognitive deterioration. Postmortem findings in HIV patients indicate extensive injury to brain white matter [(1)]. Diffusion tensor imaging (DTI) can be used to measure the overall (the apparent diffusion coefficient or ADC) and the direction-dependent (fractional anisotropy or FA) diffusion of water molecules in brain regions of interest (ROIs). These measures may confer information concerning white matter injury that cannot be detected with conventional MRI [(2)]. In this investigation, tissue status measurements were acquired for genu, splenium and lateralized frontal white matter (FWM) in HIV-infected patients and examined for patterns of relationship to cognitive status ratings from concurrent neurological (dementia severity) and neuropsychological evaluations (overall cognitive impairment).

Methods: Participants included 11 well-characterized HIV patients (age: 49.4±7.3; 9 males, 2 females) and 11 healthy controls (age: 42.4 ± 11.2; 9 males, 2 females). Dementia severity was determined according to Memorial Sloan Kettering (MSK) the American Academy of Neurology (AAN), and the Karnofsky Performance Scale. A comprehensive neuropsychological battery was used to evaluate impairment in attention, memory, constructional, motor and executive functions. Overall cognitive impairment was determined using the average of the standardized scores from the eight individual test instruments comprising the neuropsychological battery, extensively described elsewhere (see Marder et al., 1996). Subjects were scanned with a GE 1.5T MR system. DTI B_0 and DTI were obtained along six directions (TR 7000, TE 82.5, B1000). All axial slices were angle subtended (parallel) to the AC-PC line. A custom software was used to compute the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps offline. Uniform-sized ROIs were positioned by a radiologist using a well-defined and standardized placement strategy for all study subjects. Genu and splenium were identified along the midline at the plane of interventricular foramen on the axial B_0 MR image. Bilateral frontal white matter regions were identified anterior to the frontal horns of the lateral ventricles. The B = 0 reference image was used for ROI placement (rather than the diffusion images or calculated diffusion maps) in order to achieve better anatomical visibility and to reduce bias. The identified ROIs were then projected to the FA and ADC maps to acquire the DTI measurements (Figure 1).

Results: DTI measurements for each region were compared in HIV and control groups using separate analysis of variance models in with age entered as a covariate. All statistical tests used a significance level of 0.05 and were executed in SPSS (release 10.0; Chicago, IL). FA measures for splenium were significantly reduced in the HIV patients (p=.023). ADC measures for splenium were significantly increased in the HIV patients (p=.050); a nearly significant difference in ADC was noted for genu (p=.08) (Figures 2-3). There were no significant differences for DTI measures for FWM regions. Further analyses examined associations between the DTI measures and dementia severity ratings (AAN, MSK and Karnofsky) and a measure of overall cognitive impairment based on the average of cognitive functions assessed in the neuropsychological evaluation. Reduced FA measures for splenium were significantly associated with dementia severity as indicated by MSK (rho= -.53, p=.012), AAN (rho= -.52, p=.015) and Karnofsky (rho= .44, p=.042) ratings (Table 1). Increased ADC measures in corpus callosum regions were significantly correlated with overall cognitive impairment (splenium: r=-.56; p=.007; genu: r=-.51; p=.016) (Table 2).

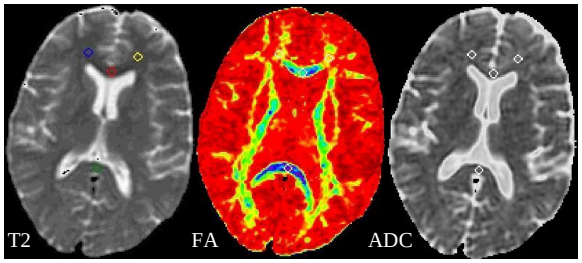
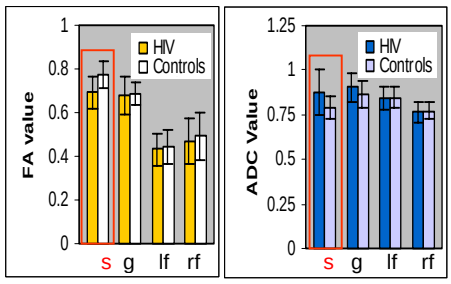


Figure 1: Uniform sized ROIs were placed on anatomical T2 Weighted Image, then projected to FA and ADC maps



Figures 2-3: FA and ADC Values (Mean and SD) of 11 HIV and 11 control subjects in four white matter regions. s: splenium g: Genu lf: left frontal white matter rf: right frontal white matter. (ADC unit 10 $^{-4}$ mm^2/s)

Table 1: Correlations: FA and Dementia Severity Ratings

	Splenium	Genu	LFWM	RFWM
MSK r (p)	-.53 **	.11	.00	-.19
AAN r (p)	-.52 **	-.05	.00	-.21
Kamofsky r (p)	.44*	-.12	.03	.16

Spearman correlation coefficients.* pLE..05; ** pLE.01
LFWM & RFWM: Left & Right Frontal White Matter

Table 2: Correlations: ADC and Overall Cognitive Impairment

	Splenium	Genu	LFWM	RFWM
Cognitive Impairment	-.56**	-.51*	-.26	- 0.36

Pearson correlation coefficients. * pLE.05; ** pLE.01

Conclusion: Findings from this investigation indicate that regions in the corpus callosum, particularly the splenium, are vulnerable to injury in HIV infected patients. FA values for splenium were significantly reduced and correlated with measures of dementia severity in HIV patients. ADC values for splenium and genu were increased and correlated with the degree of cognitive impairment determined by neuropsychological evaluation. It has been suggested that the vulnerability of the corpus callosum to injury in HIV infection has not been adequately recognized and that this region may be a predilection site for HIV Encephalitis foci, the pathologic correlate of HIV-Dementia [(3)]. This investigation indicates diffusion abnormalities in corpus callosum in HIV patients and these alterations are associated with the measured severity of cognitive impairment and dementia progression. Other DTI studies have reported diffusion abnormalities in splenium in HIV patients in advanced stages of immunosuppression [(4)] and in other cognitively impaired subjects [(5)]. Moreover, Simian Immunodeficiency Virus infection (SIV) studies in non-human primates demonstrate that significant changes in FA can be detected in the splenium within two weeks of initial infection [(6)]. Taken together, these findings suggest that DTI is a sensitive tool for quantifying neuroanatomic pathologic alterations in HIV infection and these alterations may represent potential markers of cognitive decline in HIV patients.

References:

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