Diffusion Tensor Imaging Detection of Early White Matter Changes in an accelerated SIV Primate Model of NeuroAIDS

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Introduction:

A significant number of HIV-infected patients develop neurological symptoms ranging from minor cognitive impairment to severe dementia (neuroAIDS), which are thought to be a result of injury to neurons in the CNS. There is a consensus that HIV enters the CNS during the early stages of infection primarily through virally infected/activated monocytes from the blood. Once in the brain, infected macrophages or microglia release neurotoxic substances that induce neuronal injury and apoptosis. Axonal injury has been associated with neurologic outcome in white matter diseases and CNS infections. However, traditional MRI is not sensitive to axonal injury (Falconer, 1994; Kulkarni, 1988). Previous DTI studies of HIV infected patients have indicated that as viral load increased, FA in subcortical white matter decreased while apparent diffusivity (ADC) values increased. Specifically, significant changes in FA and ADC have been reported for the genu and splenium in the corpus collosum (Filippi, 2007; Thurnher, 2005; Wu, 2008). Other studies have shown abnormalities in frontal white matter, parietal white matter, and internal capsule (Pomara 2001; Chang, 2008). In human studies, confounding factors such as age and alcoholism can contribute significantly to the extent of white matter change detected in HIV-infected patients by DTI (Pfefferbaum, 2007). The objective of our study was to test if diffusion tensor imaging (DTI) can be used to detect early changes in white matter integrity in an animal model of NeuroAIDS and how early these changes can be detected.

Methods:

Six rhesus macaques were infected with SIVmac251 and treated with the anti-CD8 antibody cM-T807 to deplete CD8 T lymphocytes at 6, 8, and 12 dpi. CD8+ T lymphocyte depletion permits virus to replicate unchecked, accelerating the disease. Animals were examined by MRI (3.0 T TIM Trio Siemens) prior to infection and at 2 and 4 weeks post infection (wpi). Axial diffusion tensor images (DTI) of the brain were obtained using single shot spin-echo EPI pulse sequences with TE=105ms, TR=2710ms, FOV=96mm, and a 96x96 matrix. A total of 16 slices were used with a slice thickness of 3mm. We collected the diffusion-weighted images in 120 directions, with a high b value (b = 700 s/mm2) on 120 gradient axes and a low b value (b = 0) for T2 images. Six anatomic locations were selected for analysis (figure 1): internal capsules, corona radiate, frontal white matter, genu (corpus callosum), body (corpus callosum), and splenium (corpus callosum). Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps were coregistered with the corresponding T2 anatomic image set using ANALYZE Software (Mayo Clinic). In addition, single voxel 1H MR spectroscopy (MRS) was performed in multiple brain regions (frontal and parietal cortex, basal ganglia, and white matter semiovale) using a point resolved spectroscopy (PRESS) sequence with TE/TR = 30/2500ms. Metabolite concentrations N-Acetyl-aspartate (NAA), choline (Cho), myo-Inositol (MI), and creatine (Cr) were quantified using the LCModel software package as ratios over Cr and using the unsuppressed water peak as reference. Plasma and CSF viral loads were quantified using a commercially available enzyme immunoassay (EIA) for SIVmac p27. For the serial FA, ADC, and MRS data, repeated measures analysis of variance (RM-ANOVA) in combination with Holm's t-tests was employed to isolate differences between time-points within the cohorts using JMP 7.0 (SAS, Cary, NC). A least-squares means model was used to identify correlations between the changes in metabolites and FA/ADC. This method allows for the correlation of data points that are not independent of one another, such as repeated measurements of DTI and MRS from the same animal over multiple time points.

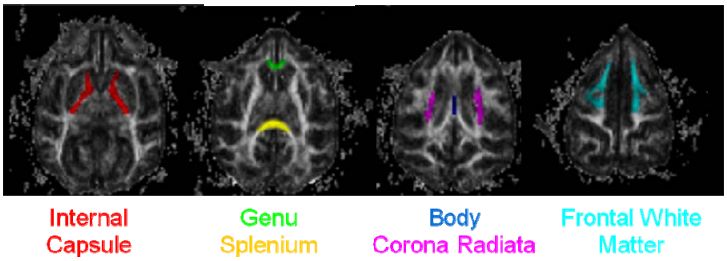
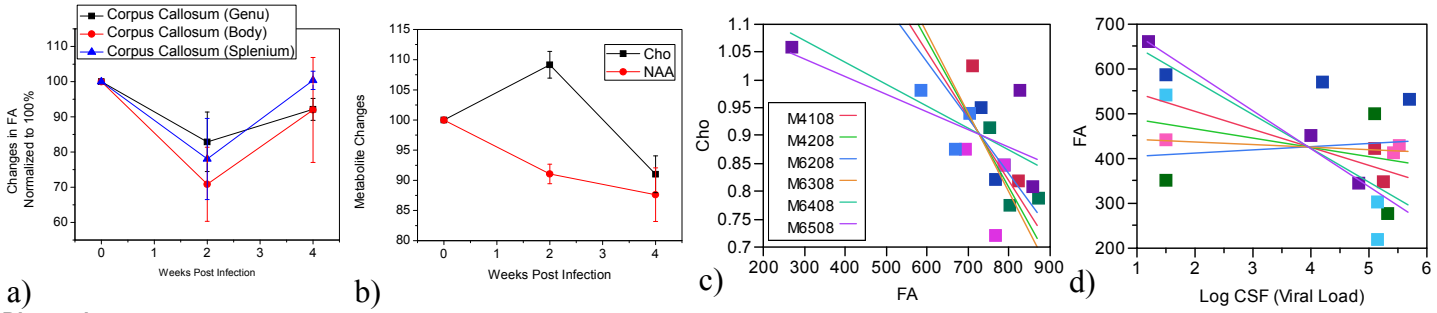


Figure 1. FA images showing regions of white matter selected for analysis.

Results:

All of the regions investigated in the corpus callosum appear to exhibit a trend of decreased FA (genu p=0.1, body p=0.07, splenium p=0.1) suggesting transient white matter damage (a). NAA/Cr decreased with SIV infection and CD8 depletion in every brain region under investigation, indicative of neuronal injury. Choline, a putative marker for glial activation or inflammation, increased at 2 wpi followed by a decrease to baseline values or below. Changes in NAA (p=0.035) and Cho (p<0.001) in the FC normalized to 100% baseline levels are shown in (b). Correlation analyses demonstrated a significant association (p=0.02) between WM damage (detected by decreases in FA) in the splenium and increases in choline (c). In addition, FA showed a negative correlation with viral load in the CSF (p=0.05), shown in (d).



Discussion:

To the best of our knowledge this is the first study using DTI to examine longitudinal brain changes prior to infection and following seroconversion. Though statistical significance was not achieved, a trend toward decreased FA at 2 weeks post infection was observed demonstrating that DTI can detect subtle transient changes in the white matter in this accelerated SIV model of neuroAIDS. We detected an inverse correlation between choline concentration and FA values in the splenium. Temporal increases in choline could reflect a first response of glial activation during acute viremia, which causes temporal changes in fiber structure reflected by decreases in FA.

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