Diffusion Tensor Imaging Detects Progressive Brain Damage in a Murine Model of Chronic HIV-1 Infection

Michael D. Boska[1], Mariano G Uberti[1], Prasanta Dash[2], Santhi Gorantla[2], Larisa Y Poleuktova[2], and Howard E Gendelman[2]

[1]*Radiology, University of Nebraska Medical Center, Omaha, NE, United States,* [2]*Pharmacology and Experimental Neurosciences, University of Nebraska Medical Center, Omaha, NE, United States*

Introduction. Chronic progressive human immunodeficiency virus (HIV) infection leads commonly to a spectrum of neurological signs and symptoms termed HIV-1 associated neurocognitive disorders. Humanized NOD/scid-IL-2Rγ_c^{null} (NSG) mice infected with HIV-1 can mirror aspects of human disease through the establishment of a human immune system, persistent viral infection, loss in CD4+ T cell numbers and induced central nervous system (CNS) pathobiology. This includes human monocyte-macrophage ingress from the periphery across the blood brain barrier, meningitis and neuroinflammation[1]. Herein, we investigated changes in diffusion tensor imaging in infected mice by assessment of fractional anisotropy (FA), mean diffusivity (D_{av}), longitudinal and transverse diffusivity ((λ_l and λ_t). We examined brain subregion alterations in FA and D_{av} in conjunction with viral load and CD4/CD8 ratios.

Materials and Methods. Newborn NSG mice were irradiated at 1 Gy then injected intrahepatically with 10^5 purified CD34+ human stem cells in 20 µl of PBS. Animals with sustained 20-50% chimerism were infected at 22 weeks of age by intraperitoneal injection of HIV-1_{ADA} using a single dose of 10^5 50% tissue culture infectious doses/ml. Infected humanized NSG mice (n=8) and uninfected controls (n=5) were imaged and had blood FACS analysis for T cell population and viral load over time from preinfection (time 0 for controls) through 4, 8, 12, and 16 weeks post infection. All procedures were done in accordance with the ethical guidelines for care of laboratory animals at the University of Nebraska Medical Center and the National Institutes of Health. Two shot respiratory gated echo planar DTI were obtained using a 7 Tesla Bruker Pharmascan system with volume coil transmit, surface coil receive, 24 mm FOV, 0.5 mm slice thickness, 96 x 96 in-plane matrix zero filled to 256 x 256, gradient balanced, rotationally invariant, alternating polarity icosahedral encoding (12 direction). Diffusion weighting parameters were b factor = 800 s/mm, δ=4 ms, Δ=15 ms, seven averages for b=0 acquisition, three averages for each b=800 encoding direction, for a total acquisition time of 20–40 min, depending on respiratory rate. Region of interest analyses were performed bilaterally in whisker barrels from reconstructed FA, D_{av}, λ_l and λ_t.

Results and Discussion. On average, mean FA decreased and mean D_{av}, λ_l and λ_t increased over time with no statistically significant difference between infected and control mice. However, the linear regressions of FA, D_{av}, λ_l and λ_t versus time in HIV-1 infected mice were strongly correlated with the degree of viremia (Fig 1). Linear regression of the values of D_{av} (Fig 1a) λt (fig 1B), λ_l (fig 1C) and FA (fig 1D) show that D_{av}, λ_l and λ_t slopes decrease (more negative slope) and FA increases with the degree of viremia as a function of time in the whisker barrels of these mice. These changes demonstrate that the mild decrease in D_{av} with viremia is largely attributable to λ_t (slope = -1 x 10^{-10}), which decreases twice as fast as λ_l (slope = -5 x 10^{-11}). These changes DTI metrics likely indicate a loss of synapses in the cortex of this mouse[1] model, most pronounced in the regions of high activity such as the whisker barrel of mice. Reductions in D_{av} have been reported with degeneration of grey matter structures[2] and during grey matter maturation[3]. These biomarkers will be used to assess the time course and effectiveness of therapies designed to combat neurodegeneration in this mouse model of HIV-1 infection, whose analysis will include levels of viremia and immunopathology.

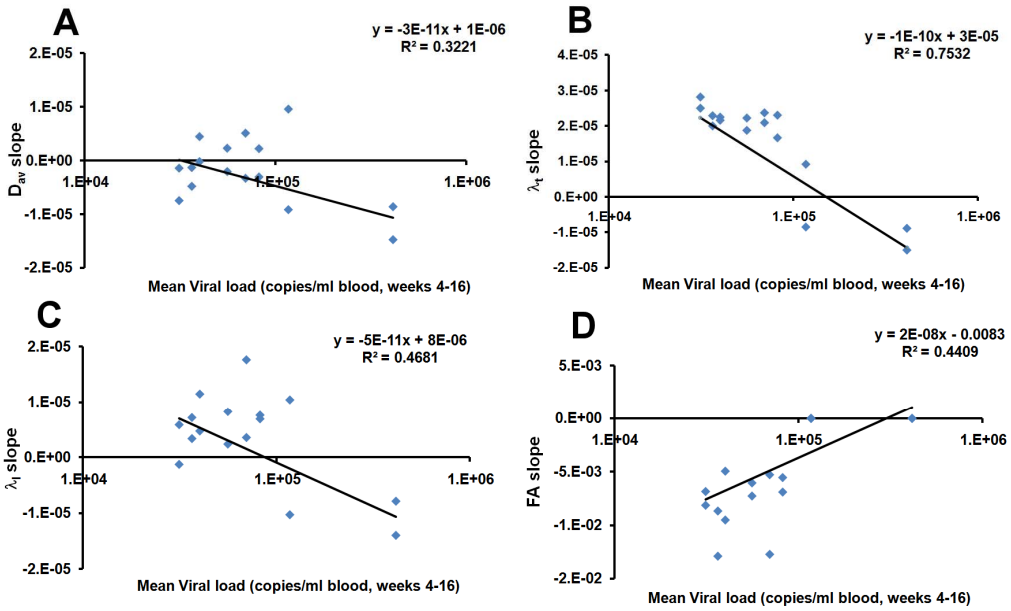

Figure 1 *Log mean viral blood concentration (X) in blood of huNSG mice from 4-16 weeks after infection versus linear regression of the A: D_{av}, B: λ_t, C: λ_l and D: FA over 16 weeks of infection.*

References:

1. Dash PK, Gorantla S, Gendelman HE, et al. Loss of neuronal integrity during progressive HIV-1 infection of humanized mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* Mar 2 2011;31(9):3148-3157.
2. Yassa MA, Muftuler LT, Stark CE. Ultrahigh-resolution microstructural diffusion tensor imaging reveals perforant path degradation in aged humans in vivo. *Proc Natl Acad Sci U S A.* Jul 13 2010;107(28):12687-12691.
3. McKinstry RC, Mathur A, Miller JH, et al. Radial organization of developing preterm human cerebral cortex revealed by non-invasive water diffusion anisotropy MRI. *Cerebral cortex.* Dec 2002;12(12):1237-1243.