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

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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-2Rα 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. Herein, we investigated changes in diffusion tensor imaging in infected mice by assessment of fractional anisotropy (FA), mean diffusivity (Dav), longitudinal and transverse diffusivity ((λl and λt)), 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 and Dav, in conjunction with viral load and CD4/CD8 ratios.

Results and Discussion. On average, mean FA decreased and mean Dav, λl and λt increased over time with no statistically significant difference between infected and control mice. However, the linear regressions of FA, Dav, λl and λt versus time in HIV-1 infected mice were strongly correlated with the degree of viremia (Fig 1). Linear regression of the values of Dav (Fig 1A) λt (fig 1B), λl (fig 1C) and FA (fig 1D) show that Dav, λl and λt 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 Dav with viremia is largely attributable to λl (slope = -1 x 10⁻⁹), which decreases twice as fast as λt (slope = -5 x 10⁻¹¹). These changes DTI metrics likely indicate a loss of synapses in the cortex of this mouse model, most pronounced in the regions of high activity such as the whisker barrel of mice. Reductions in Dav have been reported with degeneration of grey matter structures and during grey matter maturation. 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.

References: