Increased Brain Diffusion detected using DWI-MR in Cats infected with Feline Immunodeficiency Virus

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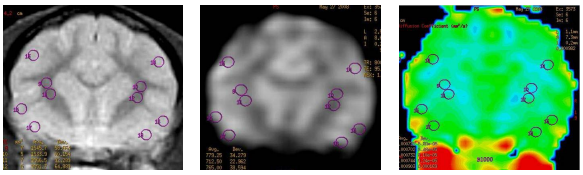
Introduction: NeuroAIDS is a poorly understood syndrome of cognitive and motor disorders than occurs in up to thirty percent of Human Immunodeficiency Virus (HIV) infections. Direct viral effects, including virus-induced neurotoxicity, and indirect effects, such as cytokine signaling and inflammatory-mediated neuroexcitatory dysfunction, have been implicated. Evidence suggests that viral genotype may play a role in the severity of neuropathogenesis of HIV infection. Partially characterized neurologic dysfunction resembling NeuroAIDS has been documented in domestic cats infected with feline immunodeficiency virus (FIV) (viral strain A-PPR), whereas a second highly immunopathogenic viral strain (C-PG) does not result in apparent neurologic disease. MRI was used to study the development of neuropathophysiology and the role of viral genotype in cats with FIV.

Methods: Specific pathogen free cats were experimentally inoculated with equivalent doses of FIV-C-PG or FIV-A-PPR, and mock-infected controls (n=5/group). MRI was performed at 4 months post-inoculation, with cats under general anesthesia maintained with isoflurane gas and positive pressure ventilation. A GE Signa LX 1.5 Tesla 9.1 MR HiSpeed Plus instrument and the quadrature head coil was used. Anatomic MRI scans included transverse dual echo proton density/T2, FLAIR, and pre- and post-contrast T1 weighted scans. Cats were also evaluated by diffusion-weighted imaging (DWI) (b values = 1000, 1500, 2000) of the entire brain, and also by multivoxel proton spectroscopy centered at the level of the thalamus (TR 1500, TE 135 ms, 10 mm thk). Apparent diffusion coefficients (ADC) were quantitated for numerous brain regions-of-interest using commercial software (Functool, GE) (Figure 1). MR spectra were analysed off-line using LC Model software for statistical analysis. Post-mortem histopathological examinations and proviral load determinations by PCR from two regions of brain were also determined at 6 months PI. Statistical analysis included repeated measures ANOVA for brain region and viral strain, Tukey's test for pairwise comparison between viral strains by brain region and two sample t-tests for pairwise comparisons.

Results: No abnormalities were visualized on the anatomic MRI scans. For all 3 b values, ADC was significantly increased in cats infected with both FIV viral strains in multiple brain regions, which varied by viral-strain (Figure 2). No significant differences were noted between groups for Choline/creatine or N-acetyl aspartate/creatine ratios. All FIV cats had low brain proviral loads and minimal histopathology (mild degree of meningeal lymphocytic infiltrate).

Conclusions: Both viral strains were associated with increased tissue water diffusion by DWI, despite only subtle histopathologic changes and low brain proviral load, a characteristic also described in human NeuroAIDS patients. These findings demonstrate that: (i) FIV is a relevant animal model for studies of NeuroAIDS pathogenesis; (ii) DWI is a sensitive indicator of FIV-associated NeuroAIDS; and, (iii) two strains of FIV varied regionally in neuropathophysiology. A second ongoing temporal study is now being conducted to evaluate the post-inoculation timing of alterations such as ADC on MRI and to further evaluate role of FIV genotypes in development of lentiviral neuropathy.

Acknowledgements: This work was supported by NIAID A1048411 and a Merck-Merial Summer Fellowship Award.



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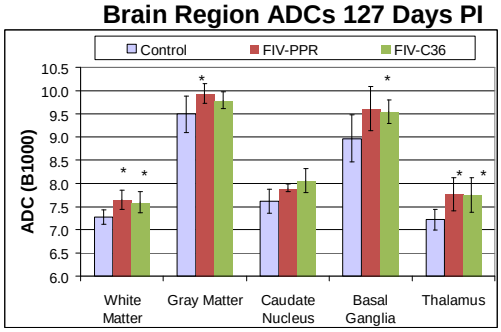
(a) Proton-density MRI, (b) diffusion-weighted MRI and (c) apparent diffusion coefficient map showing regions of interest used for sampling



Significant differences were noted between groups within brain regions in a strain-dependent manner (ANOVA: $p < 0.05$)
* = significantly different from control (Tukey's test: $p < 0.05$)