

MEMRI Reflects Human Neuropathology in a Murine Model of neuroAIDS

Aditya N Bade¹, Santhi Gorantla¹, Prasanta Dash¹, Edward Makarov¹, Larisa Y Poluektova¹, Howard E Gendelman¹, Michael D Boska^{1,2}, and Yutong Liu^{1,2}
¹Pharmacology and Experimental neuroscience, University of Nebraska Medical Center, Omaha, NE, United States, ²Department of Radiology, University of Nebraska Medical Center, Omaha, Omaha, NE, United States

Introduction: Progressive HIV infection commonly leads to cognitive impairments for HIV associated neurocognitive disorders (HAND). Disease complexity is reflected by co-morbid conditions such as substance abuse, psychiatric disease, aging and society and environment factors. To date, no reliable diagnostic tests for HAND are available despite considerable research efforts. To this end, we previously demonstrated that MEMRI detects abnormal signal enhancement in a mouse model of HAND¹. However, whether MEMRI would be broadly useful in assessing specific neurostructural inflammation related damage has not been determined. Thus in this study we employed a newly generated brain atlas² to investigate structural deficits in the brain following chronic HIV-1 infection of humanized NOD/scid- γ_c^{null} (NSG) mice.

Methods and Materials: *Animals:* NSG mice were reconstituted with CD34+ human hematopoietic stem cells (HSC) isolated from cord blood (humanized mice) then infected with HIV-1 (n = 6). Controls were humanized uninfected mice (n = 7). *MEMRI:* MEMRI was performed 16 weeks after viral infection and prior to MnCl₂ injection. Fifty mM MnCl₂ was administered ip four times at 24 hr intervals before MRI. Before injections and again at 24 hr following the final injection, MRI was performed on a 7T/21 cm Bruker Biospec (PV 5.1, Avance III hardware). 3D high resolution isotropic T₁-wt MRI and progressive saturation T₁ mapping was collected. *Data Analysis:* Brains were first subimaged from the T₁-wt MRI. Signal intensity was calibrated using T₁ values determined by T₁ mapping. Brains were then registered to a MEMRI based NSG mouse brain atlas². The Mn²⁺ enhancement ratio between MEMRI and baseline scans was calculated by subtracting baseline images from MEMRI and then normalized to measured T₁ changes. *Flow Cytometry:* FACSDiva was used to track blood human immune cell profile throughout the period of infection. *Viral Load:* The automated COBAS Amplicor System V1.5 (Roche Molecular Diagnostics) was used to measure peripheral level of viral RNA copies/ml. Following MRI scans, mice were euthanized, and brains were collected for immunohistological analysis.

Results and Discussion

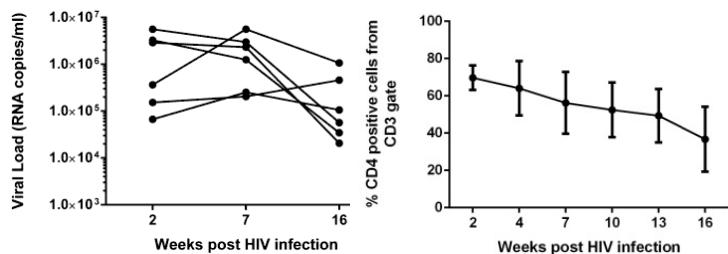


Fig.1. (a) Viral load in plasma and (b) CD4 cell populations in peripheral blood in HIV-1 infected mice

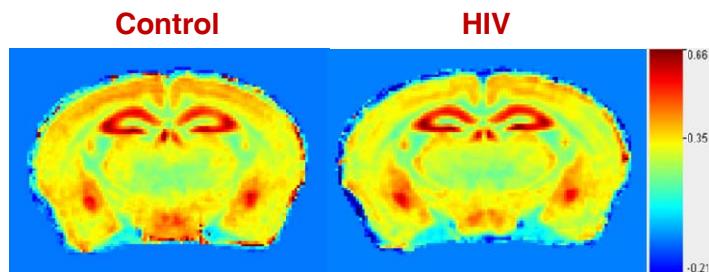


Fig.2. MRI signal enhancement ratio maps

Robust plasma viral load and human CD4⁺ T-cell decline over time were the hallmark of mice HIV-1 infection (Fig.1). Fig. 2 shows a typical Mn²⁺ enhancement map after 16 weeks of infection. Decreased enhancement on amygdala, epithalamus, hypothalamus and cortex were found. Structure-wise analysis showed significantly decreased enhancement in brain regions associated with memory/learning (hippocampus), anxiety (amygdala), motivation and olfaction (olfactory bulb) in infected mice (Fig. 3). Two mice with persistent high viral load through the course of infection showed the greatest decrease in signal enhancement, accompanied by infiltration of human cells into the brain parenchyma. **Conclusion:** The humanized mouse model reflected human HIV-1 infection profile. Decrease in signal enhancement suggests neuronal impairment in brain regions, and corresponds with HIV viral load and changes in immune cell profiles. We conclude that MEMRI is a sensitive method for detecting HIV-associated neuronal impairment and can be used to monitor therapeutic efficacy to combat neuronal damage in HAND.

References: 1. Bade, ISMRM 2013; 2. Sajja, ISMRM, 2013

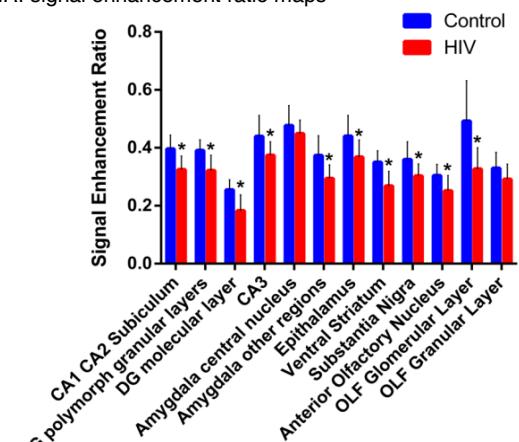


Fig.3. MEMRI Signal Enhancement Ratio compared in between several brain regions