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MEMRI Reflects HIV-1-Associated Human Pathobiology in a Rodent NeuroAIDS Model

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Abstract

Background: Progressive human immunodeficiency viral (HIV) infection commonly leads to a constellation of cognitive, motor and behavioral impairments. While antiretroviral therapy (ART) reduces disease severity, it does not affect disease prevalence. There are no diagnostic biomarkers for neuroAIDS and co-morbid conditions must first be excluded. To this end, we applied manganese (Mn^{2+})-enhanced magnetic resonance imaging (MEMRI) to noninvasively assess virus-induced neuropathology in a human disease relevant rodent neuroAIDS model.

Methods: Humanized mice (NOD/scid-IL-2Rγcnull) reconstituted at birth with human CD34+ hematopoietic stem cells were infected with HIV-1ADA (i.p. at 104 TCID50) at 22 weeks of age. Infection was followed for 16 weeks. Uninfected humanized mice used as controls. Flow cytometry for peripheral blood leukocytes was performed at 2, 4, 7, 10, 13 and 16 weeks post infection (WPI) to determine proportions of peripheral human immune cells. Plasma viral RNA copies/ml (viral load, VL) measures were performed at 2, 7, 16 WPI. Animals were MEMRI tested at 16 wpi to measure signal enhancement and morphological changes. Furthermore, an MEMRI-based brain atlas, the T1-wt signal enhancement on 41-brain regions/sub-regions was calculated and student's t-test performed to examine enhancement significance. Immunohistochemistry was performed at study termination. Brain sections were stained for human cells, virus infected human cells, neuronal, oligodendrocytes and glial inflammatory markers.

Results: CD4+ T cell decline and concomitant increases in CD8+ T cells were seen in the HIV-1 infected mice. Control uninfected animals showed no changes in cell numbers. VL values peaked at the 2nd week after HIV-1 infection and were sustained throughout the study. Human (HLA-DR+) cells infiltrated the brains of infected and control mice were seen predominantly in meninges and perivascular spaces. Few HIV-1p24+ human cells were observed. Altered MEMRI signal enhancement was readily observed in affected brain regions of infected animals. These included, but were not limited to, the hippocampus, amygdala, thalamus and cerebellum. MEMRI findings paralleled levels of infection, neuroinflammation and neuronal injury. These proved to be an accurate measure of virus-induced neuropathology.

Conclusion: These MEMRI signal enhancements demonstrates the complexities of HIV-1 associated neuropathology in rodents that reflect, in measure, the clinical manifestations of neuroAIDS as it is seen in a human host.

Results

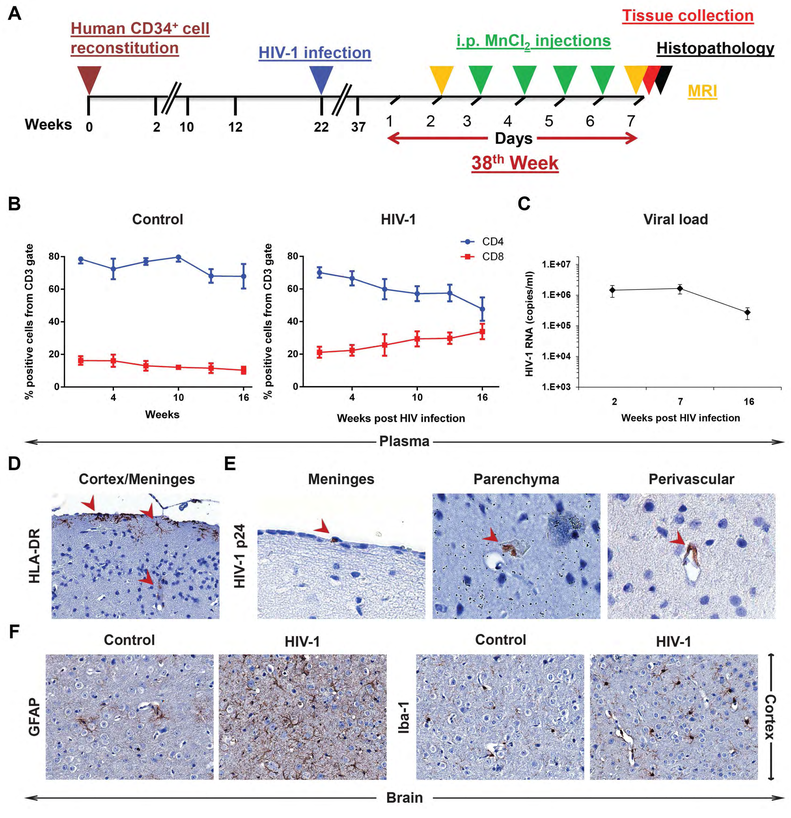
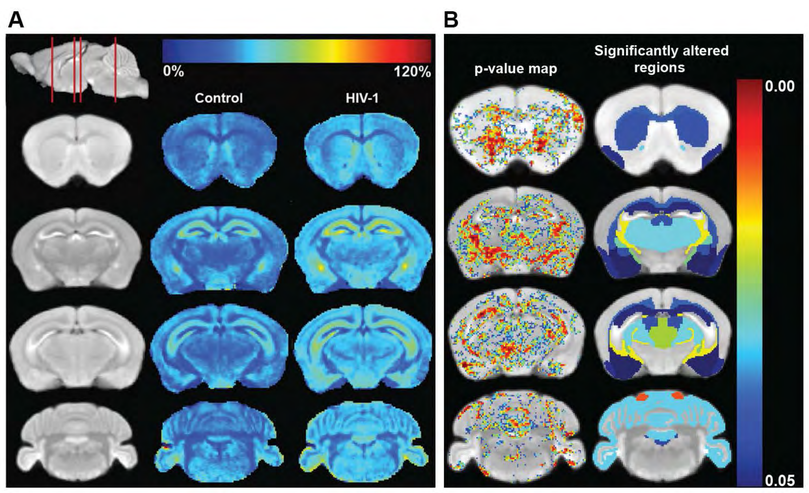


Figure 1. The time course of human CD34+ cell reconstitution, HIV-1 infection, MRI, $MnCl_2$ injections and histopathology



	Brain regions	p
Sub-cortical region	CA1_CA2_SUB	0.047
	DG-mo	0.046
	CP	0.039
	AMY	0.048
	GP	0.028
	PALc	0.047
Brain stem region	TH	0.03
	EPI	0.043
	P	0.044
	PAG	0.022
	IC	0.01
	SN	0.041
	RMB	0.033
	PRT	0.043
Olfactory region	MOBgl	0.021
	AOB	0.012
	PIR	0.046
	AON	0.036
Cerebellar region	CBXmo	0.031
Fiber tracts	cc	0.037

Figure 2. Comparison of MEMRI enhancement between HIV-1 infected animals and controls, and list of significantly altered brain regions

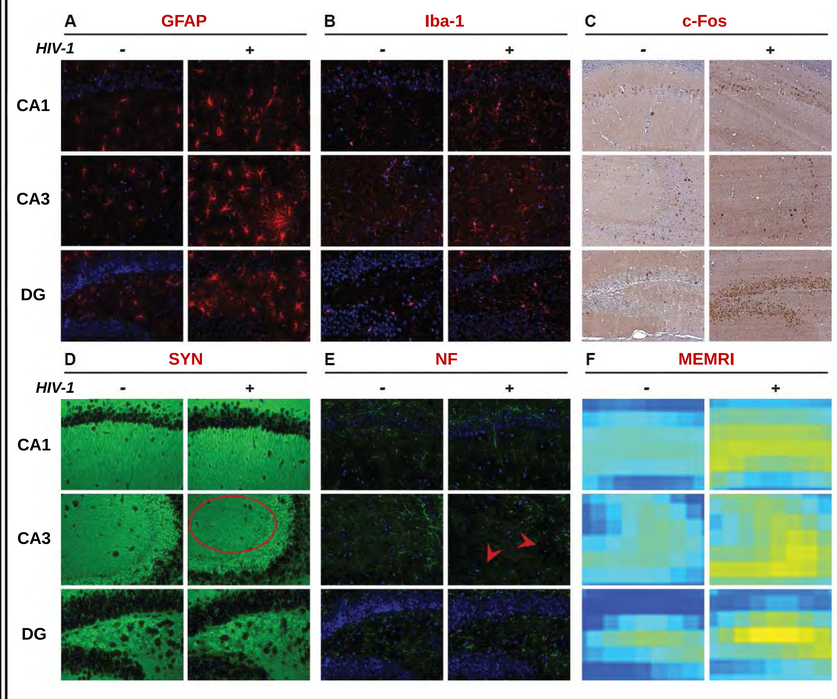


Figure 3. Immunohistology of the hippocampus sub-regions including CA1, CA3 and DG

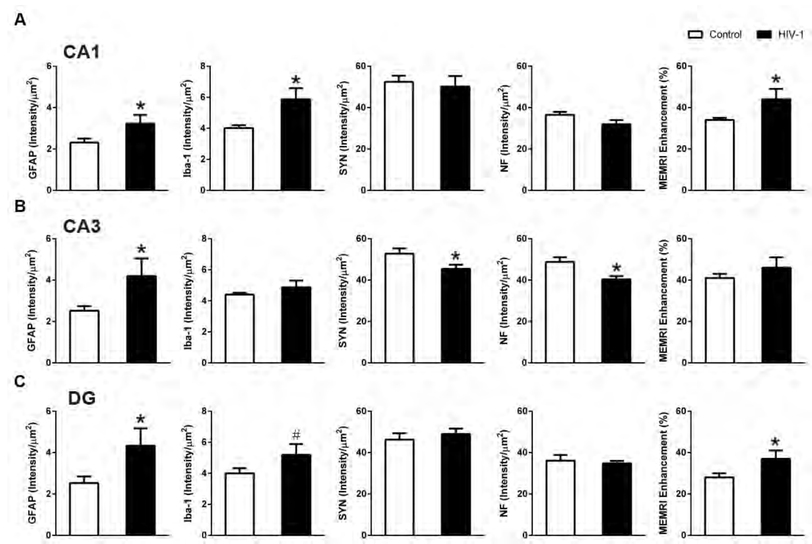
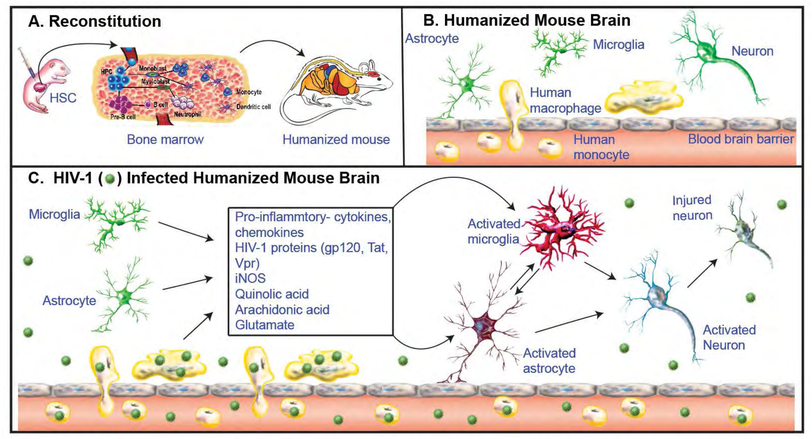


Figure 4. Association of immunohistology with MEMRI



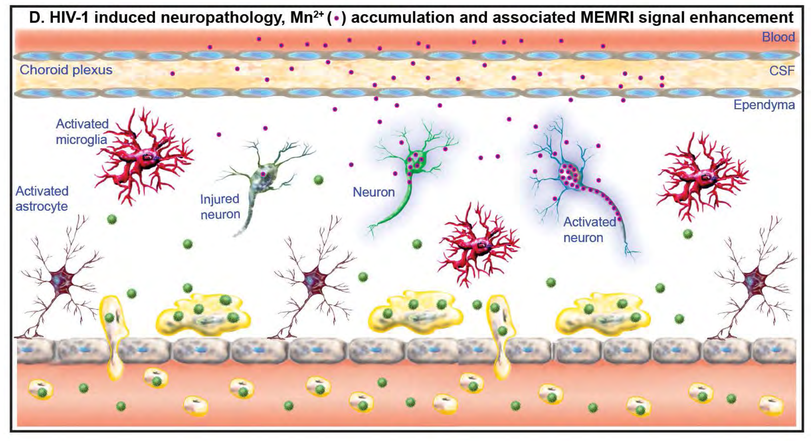


Figure 5. The mechanism of MEMRI in the detection of neuropathology in HIV-1 infected humanized mice

Conclusion

- HIV-1 infection leads to neuropathology underlying HAND in Humanized mice.
- MEMRI is a sensitive imaging tool to assess neuropathology underlying clinical manifestations of murine HAND.
- MEMRI enhancement increase is associated to reactive astrocytes and activated neurons during inflammation.
- MEMRI signal decrease is linked to neuronal injury.

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