Development of an MEMRI Biomarker for HIV-1 Infections of the Nervous System

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Introduction. A spectrum of neurological dysfunctions is associated with advanced human immunodeficiency virus type one (HIV-1) infection and termed HIV-associated neurocognitive disorders (HAND). A pathological correlate of the most severe form of HAND is a multinucleated giant cell encephalitis or HIV-1 encephalitis (HIVE). Herein, we reflected human HIVE in rodents through stereotactic injection of HIV-1-infected human monocyte-derived macrophages (MDM) into the caudate and putamen. This induced robust viral replication, gliosis (astro- and micro-gliosis), neuronal dropout and damaged dendritic arbor. Based on prior studies that showed signal enhancement in damaged brain regions during rat ischemia[1-3] we posit that MEMRI can detect early pathobiologic events in HIVE such as gliosis. Sensitivity of detection in effected brain regions was made by histological validations.

Materials and Methods. Thirty two five-week-old male NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/Sz (NSG) mice were divided into 3 groups. First (Group 1, n = 12) was HIVE injected with Mn^{2+}. Second, (Group 2, n = 8) was HIVE alone. Third, (Group 3, n = 12) NSG control mice injected with Mn^{2+}. For the HIVE mice HIV-1_{ADA}- infected MDM, 5×10^5 cells was injected in a 5 µl volume intracerebrally using stereotactic procedures[4]. The control group (Group 3) was injected with uninfected MDM. Mn^{2+} was injected through the intraperitoneal (i.p.) route 8 days before imaging and administered as a daily dose of 30 mg/kg[5]. The mice were scanned at 4, 8, 15 and 28 days after induction of HIVE using T1 mapping (fast spin echo with variable TR from 0.4 s to 10 s, 12 slices, slice thickness = 0.5 mm, in-plane resolution = 0.1x0.1 mm) and T1-wt MRI (gradient recalled echo, TR = 15 ms, flip angle = 20°, 3D isotropic resolution = 0.1 mm). Mice were euthanized after imaging was completed. At each time, 8 mice (3 from Group 1 and 3, 2 from Group 2) were MRI scanned. Brains were removed and fixed in 4% paraformaldehyde and embedded in paraffin. Five µm thick sections were cut from the paraffin blocks, mounted on glass slides, and labeled with mouse monoclonal antibodies (Dako) for HLA-DQ/DP/DR (clone CR3/43; 1:100) HIV-1 p24 (clone Kal-1; 1:10), and glial fibrillary acidic protein (GFAP) (1:1000). Microglia were identified with rabbit polyclonal antibodies to ionized calcium binding adaptor molecule 1 (Iba-1) (1:500).

Results and Discussion. On Day 4 after cell injection, no specific signal enhancement was observed at the cell injection sites in any of the animal groups. On days 8 and 15, signal enhancement was observed at the injection sites in Group 1 (Fig. 1). The injection line is shown by arrows in Fig. 1. The signal was enhanced in several regions at the injection line compared to the surrounding tissue and the regions in the contralateral hemisphere. No obvious enhancement was observed in Groups 2 and 3. Fig. 2 shows a mouse in Group 3. The MRI signal intensity about the cell injection line was similar to that in the surrounding tissue, and comparable to the signal in the contralateral side. The immunohistological results (Fig. 3) showed MDM around the injection. The infection, astrocyte and microglial activation were obvious at the cell inject site. Our results showed signal enhancement on or around the injection line in the HIVE mice during MEMRI investigation. HIV-1 infection and glial activation were found at the same regions. Our results from an in vitro comparative study of Mn uptake by glia and neurons (not shown) suggested that activated glia does not directly induce signal enhancement in MEMRI, but causes increased neuronal Mn uptake. The signal enhancement in this study may result from the increased neuronal Mn.

Refs: 1. M. Wideroe, et al., Neonatology, 2011; 2. M. Wideroe, et al, Neuroimage, 2009; 3. Y. Kawai, Neuroimage, 2010; 4. Y. Persidsky, et al., Am J Pathol., 1996; 5. B. Grunecker, NMR in Biomed, 2009

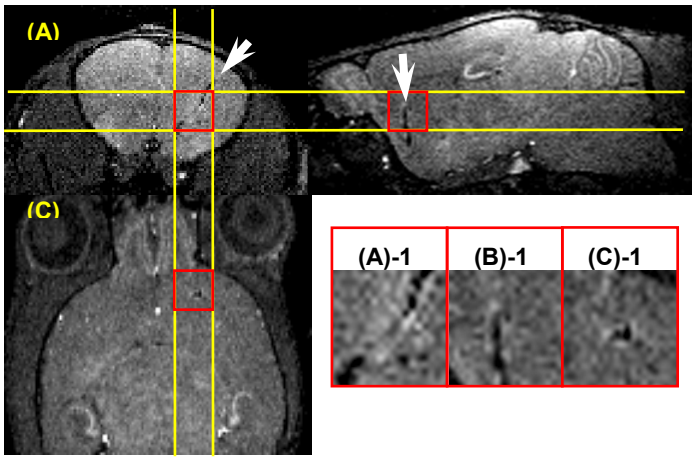

Fig.1. MEMRI of a mouse with HIVE (in Group 1) scanned at day 8 shown in (A) coronal, (B) sagittal and (C) axial views. Arrows indicate the MDM injection line. The inject site in the red boxes were shown in details in (A)-1, (B)-1 and (C)-1.

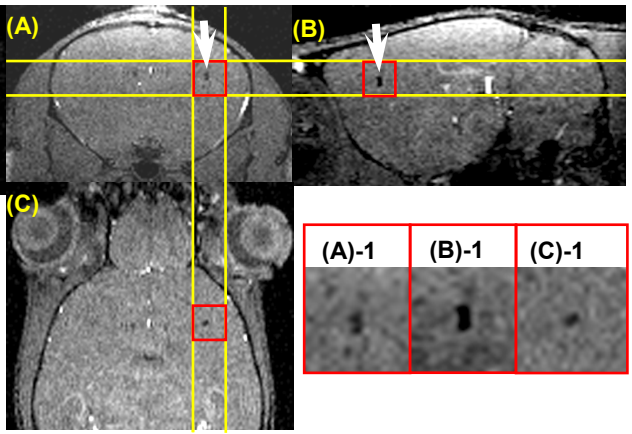

Fig.2. MEMRI of a mouse with uninfected MDM inject (in Group 3) scanned at day 8. Arrows indicate the MDM injection line.

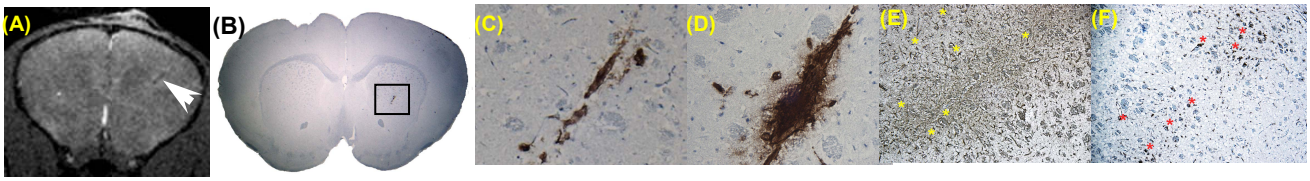

Fig.3. (A) T1-wt MRI, (B) histological slice, (C)-(F) HLA/DR, HIV-1 P 24, GFAP and Iba-1 staining in the box region in (C). The asterisks indicate activated glia