Early cerebral MR perfusion changes in the acute SIV infection primate model of neuroaids

J. He[1], H. D'Arceui[1], J. Greco[1], M. Lentz[1], E. Ratai[1], J. Kim[1], R. Fuller[1], P. Sehgal[2], S. Westmoreland[2], K. Williams[3], A. de Crespigny[1], R. G. Gonzalez[1]

[1]Massachusetts General Hospital, Boston, MA, United States, [2]NERPRC, Southborough, MA, United States, [3]BIDMC, Boston, MA, United States

Introduction: The SIV-infected macaque is an excellent animal model for studying the neuropathgenesis of HIV-related brain injury (1-2). SIV is the closest known relative of HIV, and like HIV, it infects $CD4^+$ lymphocytes, macrophages and microglia, crosses the blood-brain-barrier (BBB) and enters the CNS early in the post-infection period, causing an immediate inflammatory reaction. The primary macrophage lineage cell type infected by SIV is the perivascular macrophage (3). On the other hand, magnetic resonance imaging (MRI) continues to be one of the best probes to study the brain in vivo, especially diffusion and perfusion MR (4-5). Our goal was to use perfusion imaging to detect early functional abnormalities during the acute stage of SIV infection and illustrate possible supportive evidences to the current neuropathogenesis of AIDS.

Methods: 13 rhesus macaque monkeys (*Macacca mulatta*) were included in this study. All animals were housed and used according to the standards of the American Association for Accreditation of Laboratory Animal Care. Animals were subdivided into 2 groups according the SIV model. Group I: 8 cases, SIV mac251 model (inoculation with SIVmac251); group II: 5 cases, $CD8^+$ depletion model (animals were given anti-$CD8^+$ monoclonal antibody before inoculation with SIVmac251). MRI was done in a 1.5 T clinical MR scanner prior to inoculation, and at 2 and 4 weeks post-inoculation. Axial dynamic susceptibility bolus perfusion images of the brain were obtained using a single shot gradient-echo EPI pulse sequence; TE=40ms, TR=1000ms, flip angle of 60º, FOV=16 cm, and a 128x128 matrix. 9 slices (55 time points per slice location) were acquired; slice thickness = 3mm, 1mm inter-slice gap and NEX = 1. The contrast (Gd-DTPA 0.2mmol/kg) was injected manually as a rapid bolus. This data generated quantitative regional cerebral blood volume (CBV) and regional cerebral blood flow (CBF) maps (6). 3 anatomic locations were selected for the bilateral, region of interest (ROI) perfusion measurements in the frontal gray matter (GM), centrum semiovale white matter (WM) and basal ganglia (BG). The ROIs were outlined manually and used to compute the mean of the perfusion values (Fig.1). CBV and CBF values are expressed in arbitrary units, however the deconvolution procedure used ensured that the units are consistent and comparable across all the scans.

Results: There was significantly increased CBV in the 2 and 4 weeks post infection scans compared to the pre-inoculation scans in all anatomic location in group I (Fig.2). CBF changes in this group did not reach significance. In group II, there was no significant increase in CBV and CBF between the 2 and 4 weeks post infection scans and the initial scans in any of the 3 anatomic locations.

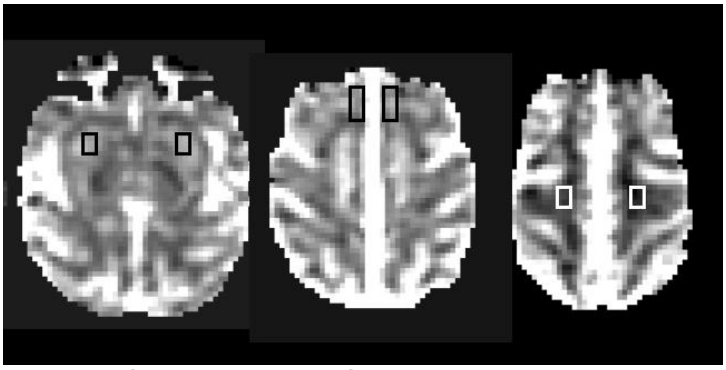

Figure. 1. Pre-infection CBV maps showing the locations of the ROIs used in the analysis.

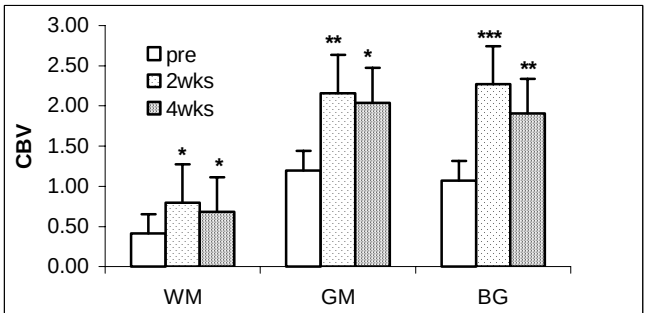

Figure.2. CBV was siginicantly increased in all 3 ROIs in the SIVmac251 model after infection (* $p<0.005$ ** $p<0.0005$ *** $p<0.00005$). Error bars represent standard error.

Discussion: The significant increase in CBV in the 2 wks and 4 wks post-inoculation animals supports the theory of a very early inflammatory reaction due to peripheral monocyte trafficking into the CNS, and developing into perivascular macrophages. Their activities are the likely cause of increased CBV in these regions. Chemokines released by macrophages and other factors such as, nitric oxide and tumor necrosis factor-alpha, which are well known vasodilators, and could effectively contribute to increased CBV. While CBV is increasing, CBF remains the same between the post-inoculation and pre-inoculation, most likely due to the so-called "auto regulation" mechanism. Longer term study will determine when this auto-regulatory effect breaks down. CBV change only occurs in the SIVmac251 infection, but not in CD8+ cell depleted SIVmac251 infection model. This interesting difference points to the specific role of the CD8+ lymphocyte in producing elevated CBV. It is possible that absence of these cells results in a weaker inflammatory reaction and hence an apparently stable CBV/CBF.

Conclusions: Our findings demonstrate solid evidence supporting the current theory of an early inflammatory mechanism in HIV/SIV pathogenesis in the CNS. It is also the first study using MR perfusion tools to probe the CNS before and during very early SIV infection, with the added advantage of knowing the exact time of infection. These preliminary but unique findings have improved our understanding of the cerebral homodynamics during AIDS neuropathogensis in vivo.

References:

1. González RG, Cheng LL, Westmoreland SV, et al: Early brain injury in the SIV macaque model of AIDS. AIDS 2000, 14: 2841-2849.
2. Greco JB, Sakaie KE, Aminipour S, et al: Magnetic resonance spectroscopy: an in vivo tool for monitoring cerebral injury in SIV-infected macaques. J Med Primatol 2002, 31:228-36
3. Williams KC, Corey S,Westmoreland SV, et al (2001). Perivascular macrophages are the primary cell type productively infected by simian immunodeficiency virus in the brains of macaques: implications for the neuropathogenesis of AIDS. J Exp Med 193: 905–915.
4. Tracey I, Hamberg LM, Guimaraes AR, et al. Increased cerebral blood volume in HIV-positive patients detected by functional MRI. Neurology 1998; 50:1821–1826
5. Chang L, Ernst T, Leonido-Yee M, et al. Perfusion MRI detects rCBF abnormalities in early stages of HIV-cognitive motor complex. Neurology 2000; 54:389–396.
6 Sorensen A, Copen W, Ostergaard L, et al. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. Radiology1999; 210: 519 –527.