CORTICAL PROTON MR SPECTROSCOPIC IMAGING ABNORMALITIES IN A MACAQUE MODEL OF NEUROAIDS

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PURPOSE: Even as highly-active antiretroviral therapy (HAART) reduces incidence of HIV-dementia, milder forms of HIV-associated neurocognitive disorders (HAND) continue to be a health concern due to complications from chronic infection. Previous quantitative MRI studies have shown HIV-related thinning of the cerebral cortex (even amongst those receiving HAART), which correlated with CD4 T-lymphocyte depletion and cognitive deficits. Multivoxel proton-MR spectroscopic imaging (1H-MRSI) studies, however, have yet to examine substantial portions of cortex. We previously reported unchanged N-acetylaspartate (NAA) in the global gray matter (GM) of simian immunodeficiency virus (SIV)-infected rhesus macaques, a well-established model system of HIV-infection. Prior histopathology, however, has revealed neuronal loss specifically in cortical regions. (It is worth noting that our previous global analyses would have averaged out all regional changes.) Consequently, in this post hoc study we test the hypothesis that early cortical SIV-infection is characterized by: (i) neuronal damage, reflected by a decrease in their NAA concentration; and (ii) glial activation, marked by increased myo-inositol (ml), choline (Cho) and creatine (Cr).

METHODS: Five (two females; 5.0 to 8.6 kg weight) healthy 3-year-old rhesus macaques (Macaca mulatta) were scanned under constant veterinary supervision, as described elsewhere. Each animal was then inoculated intravenously with SIVmac251 virus (10 ng SIVp27) and CD8+ T-lymphocyte depleted with CD8- monoclonal antibody (mAb). Two animals were rescanned 4 weeks and 3 weeks 6 weeks later. Scans were performed in a whole-body 3 T imager (Magneton TIM Trio, Siemens AG, Erlangen, Germany) using its transmit-receive knee-coil. Sagittal and axial T2-weighted turbo spin echo (TSE) MRI. TE/TR = 16/7430 ms were acquired. A 3D volumetric turbo spin echo (VIBE) (TR=35 ms) sequence (Leaving inferior–superior (IS) =28 cm³ volume-of-interest (VOI) was then image-guided and excited with dual-slab PRESS (TE/TR =33/1440 ms; Fig. 1a). Relative NAA, Cho, Cr and ml levels in the VOI’s 224 voxels – obtained with STToolsFITT package – were scaled into absolute concentrations against a 0.5 L phantom of known concentrations, as described previously. Since metabolite concentrations may vary among deep GM structures, cerebellum and cortex, we produced GM and white matter (WM) masks from the axial TSE images, as described elsewhere. We then carefully erased the striatum, thalamus and cerebellum from GM masks based on a rhesus macaque brain atlas, keeping only voxels with ≥90% total GM+WM volume fraction, as shown in Fig. 1e. We then solved for the unknown “cortical” GM metabolites’ concentrations in the remaining voxels with linear regression. Since five animals were insufficient for non-parametric tests of metabolite change, paired sample t-tests were used to assess each metabolite’s pre-to-post-infection change. Significance was tested at the p<0.05 level using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS: The ≥90% total voxel tissue constraint left approximately 450 “cortical” GM voxels (~90/animal ×5 animals) for analysis. Their mean metabolite SNRs were: NAA=25±8, Cr=16±6, Cho=10±3 and ml=10±4, which led to reliable voxel fits (all Cramer-Rao lower bounds <15%). Mean pre-to-post infection changes were: relative NAA increased 15% (7.2±0.4 to 8.3±0.7 mM, p<0.05), Cho 10% (0.9±0.1 to 1.0±0.1 mM, p<0.01); and ml 28% (5.8±0.9 to 7.4±0.8 mM, p<0.06), as shown in Fig. 1d. NAA was unchanged.

DISCUSSION: Increases in ml, a glia-specific marker, Cho and Cr reflect glial activation in cortex contained within the VOI. Elevated ml is consistent with previous neuropathology in this model, showing widespread elevations of glial fibrillary acidic protein and ionized calcium binding adaptor molecule 1 – an immunohistochemical marker of microglial activation – at four and eight weeks post-infection. Unchanged NAA, however, suggests neuronal cell bodies may be spared early on in the disease. One implication is that astrocyte/microglial activation may precede neuropathogenesis, consistent with evidence previously reported. It is also possible that WM injury at first or alone may explain cognitive deficits observed. It is noteworthy that due to presence of lipids the VOI was limited to midline/parietal cortex, ~20% of its total.

CONCLUSION: Taken together with previous findings, these results suggest treatment regimens to reduce gliosis may be helpful in preventing downstream neurodegeneration and cognitive impairment. Provided that further animal testing demonstrates safety, future HIV treatment regimens may benefit from anti-inflammatory drugs aimed at reducing gliosis as a possible therapeutic strategy against HAND.


Fig 1. Top, left (a): Sagittal T2-weighted MRI of a rhesus macaque head 4 weeks post-SIV infection showing the 3.5x4.2 cm VOI (solid lines) placement. Note the open arrow on a denotes the level of b and c. Middle, left (b): Real part of the 7x8 (LRxAP) 1H MRI spectrum on common chemical shift and intensity scales. Note the SNR and spectral resolution in those (0.5 cm³)~125 voxel counts. Bottom, left (c): A 3D view of the cortical partial volumes (beige) in a 1H-MRSI slice with voxels meeting the ≥90% total volume fraction threshold highlighted (blue). Note the absence of deep GM structures whose voxels’ contents were excluded. Right, (d): Line-plots of the NAA, Cr, Cho and ml concentration changes from pre-to-post infection scans for each animal (denoted by symbols in the key). Note the statistically significant increases (open arrows) in mean Cr and Cho, as well as a near-significant elevation in ml.