Longitudinal Evaluation of brain lesion in SIV macaques with Magnetization Transfer Imaging

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Target audience: MRI scientists and researchers on HIV/AIDS.

Introduction: Magnetization transfer (MT) imaging has been demonstrated to be a robust approach to characterize brain injury quantitatively and non-invasively in HIV infected patients [1-4]. However, the MT-imaging findings in patients with HIV may be affected with unknown conditions such as time of infection and treatment history, etc. The Simian immunodeficiency virus (SIV) infected macaque model exhibits neuropathological symptoms similar to those seen in HIV infected humans, and has been widely used for studying the cognitive and neuropathological sequelae of AIDS [5]. In this study, MT imaging was employed to evaluate longitudinal changes during SIV infection in a novel macaque model of Neuro-AIDS.

Methods: Three adult male pig-tailed macaques (Macaca nemestrina) were infected with the SIVsmmFGb, a highly neuropathogenic virus in the pig-tailed macaques [6]. MRI scans were performed on a Siemens 3T scanner with the CP extremity coil before SIV inoculation and in the weeks (2, 4, 8, 16 and 20) post inoculation (wpi). Blood samples were collected from each animal for monitoring CD4+ and CD8+ T-cells [6] at each time points. The behavioral tests [7] were carried out to evaluate cognitive functions. During MRI scanning, animals were anesthetized and immobilized with a custom-built monkey head holder. Anesthesia was maintained with 1-1.5% isoflurane. Et-CO_2, inhaled CO_2, O_2 saturation, blood pressure, heart rate, respiration rate, and body temperature were monitored continuously. The MT images were acquired using the EPI sequence with parameters: TR / TE = 3890ms/20ms, FOV= 96 × 96 mm, data matrix =64 × 64, slice thickness = 2.2 mm, 16 slices were acquired. The MTR maps were generated with the MATLAB programs constructed in-house. The MTR maps were obtained by using the formula: MTR = $(M_0 - M_s)/M_0 \times 100\%$, where M_S and M_0 are the signal intensities in a given voxel obtained with or without the RF saturation. The regions of interest were selected and calculated with the Stimulate software [2]. The cortical, subcortical and global regions were selected to acquire mean MTR for data analysis. Analysis of variance (ANOVA) for repeated measures was performed to check the differences across time points; Student's t-test was applied to compare averaged MTR values pre- and post inoculation. Correlation of CD4+ T cell and CD8+ T cell percentages, CD4/CD8 ratios, and neurological scores with MTR results were also calculated. SPSS 19.0 was used for statistical analyses.

Results: Longitudinal changes in CD4+ and CD8+ T-cell percentages are illustrated in Fig. 1. CD4+ T cell percentage decreased progressively as expected, differing significantly from the baseline at 8 and 20 wpi. The CD8+ T cell percentages were significantly increased immediately after inoculation (Fig 1). MTR histograms from whole brains pre- and post inoculation are shown in Fig.2. In comparison with the result in pre-scan, histograms in monkeys post inoculation were shifted toward the lower MTR values. MTR in the cortical, subcortical and whole brain decreased progressively after SIV infection. MTR in the cortical showed nearly significant reduction post inoculation (Fig 3). The longitudinal changes of MTR in the cortical and subcortical regions were shown in Fig 4. Significant reduction in MTR of the cortical region was observed in 16 and 20 wpi. MTR in the subcortical also exhibited decreasing tendency but did not reach statistical significance as compared with baseline; the cross-correlations of MTR in the cortical, subcortical and whole brain with CD4+ T cell percentage, CD8+ T cell percentage and CD4:CD8 ratios did not reach any statistical significance.

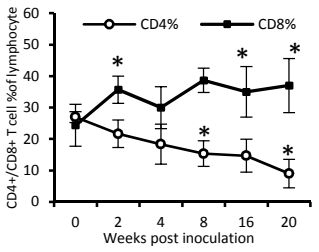

Fig.1 CD4+ and CD8+ T-cell % of lymphocyte changes in macaques after SIV inoculation. Error bars represent standard deviation error. *, P < 0.05 compared with the baseline (before SIV inoculation).

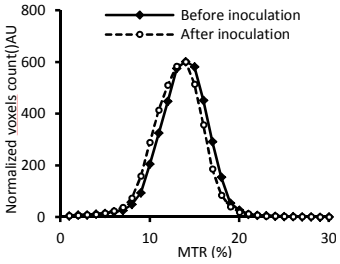

Fig.2 Histograms of the whole brain MTR before and after inoculation.

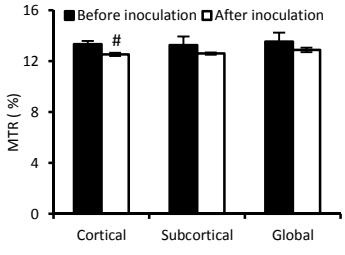

Fig.3 MTR changes of the cortical, subcortical and whole brain between pre- and post SIV inoculation. Error bars represent standard deviation error. # P=0.09

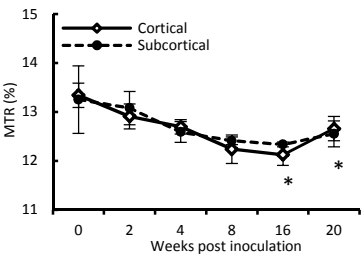

Fig.4 Longitudinal MTR changes in the cortical, subcortical after SIV inoculation. Error bars represent standard deviation error. * P<0.05 compared with baseline (before SIV inoculation).

Discussion and Conclusions: The behavior test results indicated the SIV-infected monkeys were neurologically asymptomatic in the entire study period [7]. The MTR histogram results of the SIV monkeys are consistent with that seen in HIV infected patients [4]. Also, the MTR reduction in the cortical, subcortical and whole brain is similar to that reported in patients with HIV [2, 4], though the reduction did not reach statistical significance which may be due to the small study cohort. In the longitudinal data, the significant MTR reduction was detected in cortical region in the late period (16^{th} and 20^{th} wpi), indicating that the cortical regions may be more sensitive than other regions in the asymptotic period. Correlation analysis of MTR of the cortical, subcortical and whole brain with CD4+ and CD8+ T cell percentages did not reach significant difference. In comparison with our previous results on the same group animals measured with diffusion tensor imaging (DTI) [7], the present findings suggest that MTR changes lag behind DTI parameter changes in which significant reduction in the whole brain fractional anisotropy (FA) occurred earlier than that in MTR and the whole brain FA changes significantly correlated with CD4+ T cell counts after SIV inoculation [7].

In conclusion, MTR was reduced progressively after SIV infection. The significant reduction was observed in the late study period after SIV inoculation in which the animals were still asymptomatic. The results validate the findings in HIV-infected patients that MT imaging is a robust means to access the brain injury due to HIV infection. Also it is indicated the SIV-infected monkey is an excellent model for investigating the brain tissue changes after SIV infection.

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References: [1] Grossman, R. I. Magnetization transfer: theory and clinical applications in neuroradiology, Radiographics (1994); [2] Wu, Y., et al. Whole brain and localized magnetization transfer measurements are associated with cognitive impairment in patients infected with human immunodeficiency virus. AJNR Am J Neuroradiol (2008); [3] Dousset, V., et al. Magnetization transfer study of HIV encephalitis and progressive multifocal leukoencephalopathy. AJNR Am J Neuroradiol (1997); [4] Ge, Y., et al. Whole brain imaging of HIV-infected patients: quantitative analysis of magnetization transfer ratio histogram and fractional brain volume. AJNR Am J Neuroradiol (2003); [5] Williams et al. Nonhuman primate models of NeuroAIDS. J Neuroviral (2008); [6] Francis J. Novembre et al. Isolation and characterization of a neuropathogenic simian immunodeficiency virus derived from a sooty mangabey. Journal of Virology (1998); [7] Li et al, Longitudinal diffusion tensor imaging and perfusion MRI investigation in a macaque model of neuro-AIDS: a preliminary study. Neuroimage (2011)