Regional cerebral blood flow changes of a SIV-infected monkey Model of Neuro-AIDS

C-X. Li[1], X. Zhang[1], A. Komery[2], F. J. Novembre[2], and J. G. Herndon[3]
[1]Yerkes Imaging Center, Yerkes National Primate Research Center, Emory University, Atlanta, GA,30329, United States, [2]Divisions of Microbiology and Immunology, Yerkes National Primate Research Center, Emory University, Atlanta, GA,30322, [3]Divisions of Neuroscience, Yerkes National Primate Research Center, Emory University, Atlanta, GA,30322

Introduction: Because of findings that regional cerebral blood flow (rCBF) is significantly reduced in HIV+ patients, this measure has been proposed as a non-invasive biomarker for HIV-associated CNS damage, perhaps with the potential for classifying or predicting the degree of neurocognitive impairment [1-5]. However, several factors, uncertainty of the time of infection and inter-individual variability of adherence to medication regimens, make longitudinal determination of changes in rCBF unreliable. An animal model of Neuro-AIDS obviates these problems. In the present study we employed a Simian Immunovirus Virus (SIV)-infected monkey model of Neuro-AIDS whose CNS damage closely resembling that seen in humans [6, 7]. The goal of the study was to use the continuous arterial spin labeled (CASL) MRI technique to measure to quantitatively determine the longitudinal pattern of CBF change following infection.

Methods: 3 male adult pig-tailed macaques (Macaca nemestrina) were infected with SIVsmm9 [6, 7] after the baseline data collection. Animals were sacrificed six months later. Prior to MRI scans, animals were anesthetized 1-1.5% isoflurane and their heads were immobilized in a custom-built monkey head holder; anesthesia was maintained with the same agent. O_2 saturation, blood pressure, heart rate, respiration rate, and body temperature were monitored continuously during each scan. CD4 and CD8 T-cell counts were determined in blood samples collected prior to inoculation (three times), and at 2, 4, 8, 12, 16, 20 weeks post-inoculation. Neurological examinations were also carried out at each time point. Scans employing the amplitude-modulated CASL technique were performed with a CP-extremity knee coil on a Siemens 3T Trio scanner [4]. The MRI parameters were: TR / TE = 3840/19ms, FOV= 96 × 96 mm, data matrix =64 × 64, slice thickness = 2.0 mm, post-labeling delay = 0.8 s, Labeling duration= 2 s, label offset= 50 mm. 16 slices were acquired. Each scan acquired 40 pairs of images and was repeated 3 times. The CBF maps were generated with the MATLAB programs constructed in-house, and the rCBF values were normalized. The caudate (Fig. 1, left), frontal cortices (Fig. 1, middle) and the inferior medial parietal cortex (Fig. 1, right) were selected for ROI 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 average pre- and post-inoculation rCBF values. Correlation of CD4 values, CD4/CD8 ratios, and neurological scores with rCBF results were also calculated. SPSS was used for statistical analyses.

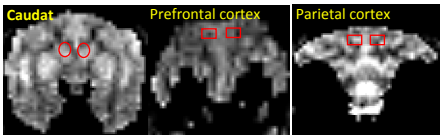

Fig 1. Monkey cerebral blood flow map acquired with CASL. ROIs were illustrated.

Table 1 Correlation between CD4, CD8 cell counts and rCBF, * P<0.05

Cell count and ratio	Caudate	Prefrontal cortex	Parietal cortex
CD4	0.48*	0.48*	0.55*
CD4/CD8 ratio	0.48*	0.33	0.71*

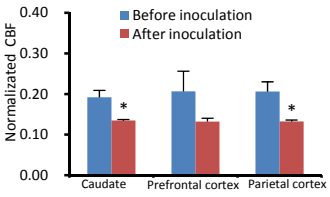

*Fig.2: rCBF changes (before and after viral inoculation) in the caudate, frontal cortices and inferior medial parietal lobe, Error bars denote standard deviation. *P <0 .05*

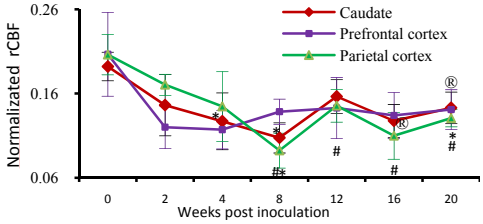

*Fig.3: rCBF changes in caudate, frontal cortex and the parietal cortex in different time points. Error bars denote standard deviation. * , #, ®, P <0 .05 compared with baseline, 2nd week and 12th week.*

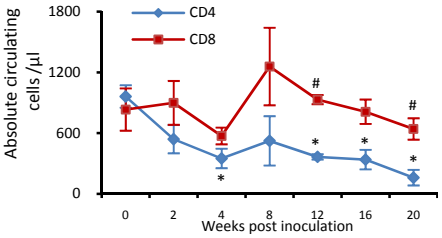

*Fig.4 CD4 and CD8 T-cell counts in SIV-infected macaques. Error bars denote standard deviation error. *P <0 .05 compared with baseline; # P <0 .05 compared with 16th week.*

Results: Under the controlled conditions of this study, rCBF values in the selected ROIs (caudate, prefrontal cortex, and inferior medial parietal cortex) declined after the SIV inoculation (Fig 2). Declines relative to baseline were statistically significant in both caudate (4th, 8th week after viral inoculation) and the inferior medial parietal lobe (8th, 20th week). The rCBF changes in the prefrontal cortex generally coincided with the changes of the CD4 and CD8 counts, but changes in the caudate and parietal cortex lagged behind slightly (Fig 3, Fig 4). In addition, the rCBF changes of the ROIs significantly correlated with CD4 counts and CD4/CD8 ratio (except prefrontal cortex) (Table 1). No abnormal behavior was observed before or after inoculation.

Discussion and conclusion: The reported rCBF reductions following SIV infection in monkeys is consistent declines reported in HIV+ patients [1-3]. Significant differences were observed in the caudate and inferior parietal cortex, but not in the prefrontal cortex. The latter negative finding may be due to small group size in this pilot study. The significant correlations of the longitudinal CBF changes with the CD4 cell counts and CD4/CD8 ratio (excluding prefront cortex) suggests sensitivity of CBF to disease development. The findings suggest that the CBF may be a sensitive surrogate marker for studying SIV induced brain impairment mechanism and medication development. Further studies with a larger group of monkeys should reduce the variance of the rCBF values and blood cell counts and improve the correlation between them. In conclusion, CASL provides non-invasive and absolute quantitative measurement of CBF with the monkey models of Neuro-AIDS, and is suitable for measuring the progressive neural change following SIV infection. The rCBF changes correlate well with the depletion of CD4 and can be a sensitive surrogate biomarker for characterizing the disease and treatment development.

References: [1] Maini et al, Nucl Med Commun.(1990); [2] Ances et al, Neurology (2006, 2009); [3] Chang et al, Neurology (2000); [4] Wang et al, Radiology (2005); [5] Tucker et al, J of Neuroimmunology (2004); [6] Novembre et al. J of Virology (1998); [7] O'Neil et al, Am J Pathol (2004);