Decreased Brain Glx Levels in HIV Dementia: A 3 Tesla MR Spectroscopy Study

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Introduction: The pathophysiology of HIV-associated dementia (HAD) has been extensively studied in the past using MR spectroscopy (MRS) at 1.5 Tesla (1). At higher magnetic field strengths (such as 3.0T), increased sensitivity and chemical shift dispersion allow for more reliable determination of compounds such as glutamate (Glu) and glutamine (Gln) compared to 1.5T (2). The current study was undertaken to investigate the utility of 3T MRS for evaluating HIV+ patients with different levels of cognitive impairment with emphasis on the measurement of Glu and Glx (the sum of Glu and Gln).

Material and Methods: Eighty-six HIV+ subjects were stratified into 3 groups according to their cognitive status using the Memorial Sloan Kettering (MSK) dementia severity score. Twenty one with normal cognitive function (NC) (MSK 0), 31 had mild cognitive impairment (MCI) without dementia (clinical MSK stage = 0.5) and 34 had dementia (HAD) (MSK ≥1). Using a 3.0T Philips scanner and SENSE head coil, brain MRI and single voxel MRS (TR/TE=2000/45 msec) were acquired from the left frontal white matter (FWM) and the left basal ganglia (BG) with and without water suppression. The voxel size was 2.2x2.2x2.2 cm^3. Spectra were analyzed using the LC model (3) and quantified (in mM concentrations) relative to the unsuppressed water signal. Metabolite concentrations and ratios relative to creatine (Cr) were calculated for the 3 groups. Differences between groups were evaluated using ANOVA and post-hoc comparisons. $P < 0.05$ was considered significant.

Results: FWM Glx (combined Glu and Gln) was lower in HAD (8.1±2.1 mM) compared to both MCI (9.17±2.1 mM) and NC group (10.0±1.6 mM), (P = 0.006). FWM mI was higher in HAD (4.15±0.75 mM) compared to both MCI (3.86±0.85 mM) and NC status (3.4±0.67 mM), (P = 0.006) (Figure a). FWM Glx/Creatine (Cr) was lower and FWM myo-inositol (mI)/Cr significantly higher in the HAD compared to MCI and NC group ($P = 0.01$) and ($P = 0.004$) respectively (Figure b). BG NAA was lower in the HAD group (6.79±1.53 mM), compared to the MCI (7.5±1.06 mM), and NC groups (7.6±1.01 mM), ($P = 0.036$). There were significant positive correlation of FWM Glx with Digit symbol test (P= 0.02, 0.002, and 0.02 respectively) (Figure c). There were also significant negative correlations between Glu, Glx, and Glx/Cr with trail-making test B (P= 0.005, 0.0001, and 0.0003 respectively) (Figure d). FWM Glx showed negative correlation with Grooved pegboard non-dominant hand (P= 0.02) (Figure e).

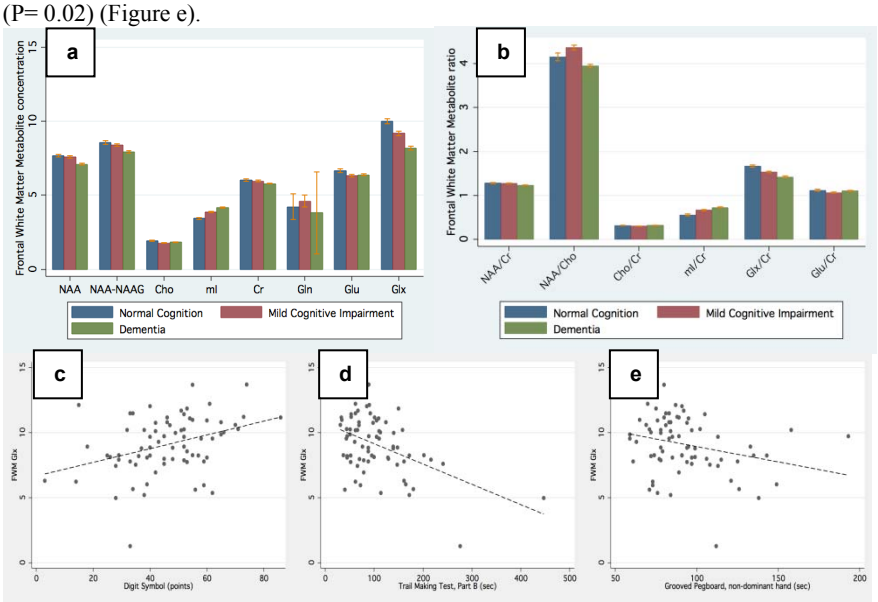

Figure: (a) showing the metabolite concentrations (b) ratios in the FWM in HIV+ patients with normal cognition (NC), mild cognitive impairment (MCI) and with HAD, (c) positive correlation of FWM Glx with Digital symbol, (d) negative correlations of FWM Glx with Trail Making Test, Part B, and (e) negative correlations of FWM Glx with Grooved Pegboard non-dominant hand.

Discussion and Conclusion: Several studies performed at 1.5T have previously reported reduced FWM NAA and increased mI/Cr levels in HAD, suggesting neuroaxonal loss or dysfunction, and glial proliferation, respectively (1). The current study is consistent with these prior reports. In addition, 3T MRS with phased-array head coil reception allows more sensitivity detection of MRS metabolites (in particular compounds such as Glx), and it appears that Glx (consisting of mainly Glu) is abnormal in FWM of patients with HAD. Reduced Glu uptake has previously been demonstrated to occur *in vitro* in astrocytes exposed to HIV as detected by Northern blot analysis and immunoblotting (4), and was recently reported in a cohort of 13 HIV positive subjects using TE-averaged MRS at 3T (5). In the current study, in a large cohort of HAART experienced HIV+ individuals, progressively decreasing levels of FWM Glx were found in patients with normal cognition, MCI, and HAD. FWM Glx decreases were also associated with poorer cognitive function, specifically impaired executive and fine motor functioning in HAD. 3T MRS measurements of Glx may be a useful indicator of neuronal loss or dysfunction in patients with HIV infection.

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