Age-Related Changes in Brain Metabolites in Antiretroviral Medication-Stable HIV Patients

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INTRODUCTION: Human Immunodeficiency Virus (HIV) infection may alter the pattern of changes in brain metabolism with aging [1-3]. Due to new antiretroviral medications, many more HIV-infected people have longer or normal life expectancy. Therefore, the influence of both the HIV status and the medications on their aging process has become a concern. The aim of this study is to investigate the interaction between HIV status and aging on brain metabolites in medication-stable HIV subjects using ^{1}H MR spectroscopy (MRS).

METHODS: Fifty-two subjects were studied: 18 seronegative controls (SN: 4F/14M, age 47 ± 12 years, education 16 ± 2 years), 18 seropositive neuroasymptomatic subjects (HIV-NA: 2F/16M, age 45 ± 7 years, education 14 ± 2 years, clinical AIDS Dementia Complex or ADC stage 0), and 16 seropositive subjects with cognitive deficits (HIV-CD: 1F/15M, age 53 ± 8 years, education 15 ± 3 years, clinical ADC stage 0.5-1.0). HIV+ subjects were on stable antiretroviral medications. Localized ^{1}H MRS was performed on a 3 Tesla MR scanner (Siemens MAGNETOM Trio, Siemens AG Medical Solutions, Erlangen, Germany) in four brain regions: medial frontal gray matter (GM), right frontal white matter (WM), right basal ganglia, and medial parietal GM, using a standard Point RESolved Spectroscopy (PRESS) acquisition sequence (TR/TE = 3000/30ms, 64 averages). Additional water T2 data were acquired in conjunction with LCModel analysis to obtain metabolite concentrations [4-5].

RESULTS: The two HIV groups had similar disease severity, including CD4 counts (HIV-NA: 479 ± 240 /μL; HIV-CD: 385 ± 202 /μL), nadir CD4 counts (HIV-NA: 152 ± 121 /μL; HIV-CD: 140 ± 123 /μL), log plasma viral loads (HIV-NA: <2.2 ± 1.1, 13 subjects had undetectable load; HIV-CD: <2.5 ± 1.4, 11 subjects undetectable), HIV Dementia Scale (HIV-NA: 15 ± 1; HIV-CD: 13 ± 2), Karnofsky Score (HIV-NA: mean = 97, range 80-100; HIV-CD: 88, 70-100), and duration of medication (HIV-NA: 34 ± 26 mo.; HIV-CD: 40 ± 32 mo.). Significant MRS findings are summarized in **Fig. 1**. Compared to SN, the HIV+ subjects showed increased frontal WM *myo*-inositol concentration ([mI], HIV-NA: +17%, p = 0.03; HIV-CD: +17%, p = 0.02). HIV-CD also showed decreased basal ganglia N-acetylaspartate concentration ([NAA], -13%, p = 0.01) and glutamine+glutamate concentration ([Glx], -15%, p = 0.01), and HIV-NA showed similar trends. There was a significant status x age interaction for the frontal GM [NAA] (p = 0.03) and [Cho] (p = 0.04); see **Fig. 2**. In the SN controls, increases in [Cho] with age were observed at a rate of 8-10% per decade in the frontal GM (0.15 mM/decade, p < 0.01), the basal ganglia (0.17 mM/decade, p < 0.01), and the parietal GM (0.09 mM/decade, p < 0.02). Similar age-related increases in [Cho] were observed in the frontal GM (0.16 mM/decade, ~9%/decade, p < 0.05) of HIV-NA. However, no significant change in [Cho] with age was observed in the frontal WM in any of the three groups. In the SN controls, [NAA] increased at a rate of 3-4%/decade in the frontal GM (0.32 mM/decade, p < 0.05) and the frontal WM (0.25 mM/decade, p < 0.05), and at a rate of 9%/decade in the basal ganglia (0.72 mM/decade, p < 0.01). In HIV-NA, the frontal GM [NAA] increased at a much higher rate (0.81 mM/decade, 9%/decade, p < 0.0001). No significant change in [NAA] with age was observed in the parietal GM in any group.

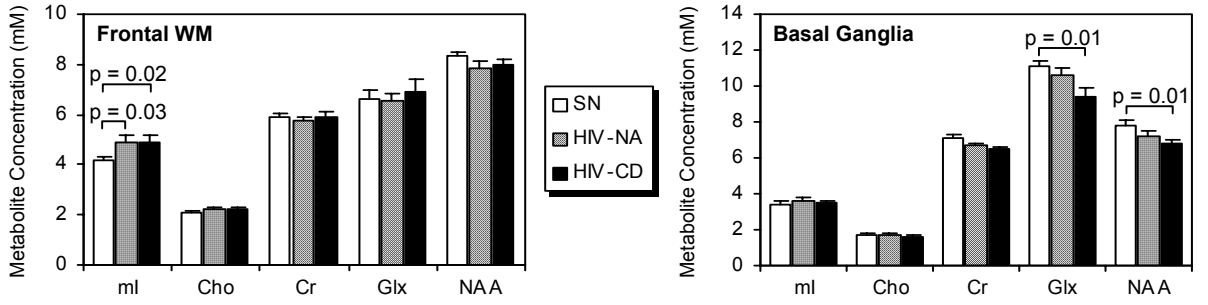

Fig. 1. Change in brain metabolite concentrations (mean+SE) in HIV subjects.

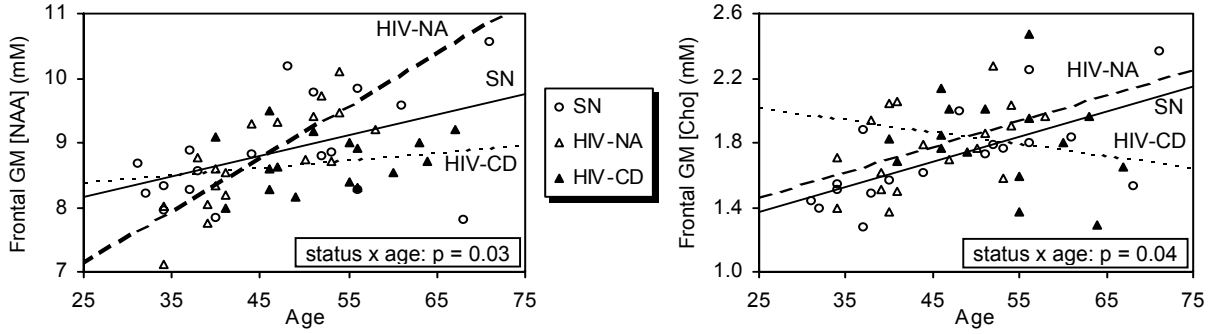

Fig. 2. Regression plots with significant HIV status x age interactive effect on metabolite concentrations.

DISCUSSION: A trend for age-related increases in frontal [NAA], particularly in the GM, has been observed in healthy aging [6-7]. However, the age-related increase in basal ganglia [NAA] in our HIV-NA subjects is different from a prior report [1], which may be due to the greater proportion of female control subjects in the prior study. The slower rate of age-related increase in [NAA] in the HIV-CD group suggests a greater age-related neuronal injury in the frontal cortex, as reported in patients with ADC [3]. The finding of age-related increases in GM [Cho] in both SN and HIV-NA, but not in HIV-CD, suggests a greater glial activation in GM-rich regions during healthy aging, but the HIV-CD patients may have a depressed neuroimmune response. Furthermore, the differences in the age-related changes in metabolite concentrations between these antiretroviral-treated subjects and the medication-naive HIV subjects in the prior study [1] indicate that antiretroviral medications may modulate the effects of HIV on the aging brain.

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