Lower NAA Correlates with CD16+ Monocyte Expansion During Primary/Early HIV Infection

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Introduction: A leading hypothesis of neuroAIDS pathogenesis states that specific subsets of bone marrow derived blood monocytes (CD14/CD16) traffic into the central nervous system, become perivascular macrophages, and initiate a cascade of events resulting in neurological disease. Several proton magnetic resonance spectroscopy (^{1}H MRS) studies have revealed neuronal injury (lower NAA) and inflammation (higher Cho or MI) in the chronic stage of HIV infection [1]. This damage may result from infected and/or activated peripheral blood monocytes coming into the brain at an earlier timepoint. During primary (acute) infection, the SIV/macaque model has suggested that viral entry into the CNS [2] and changes in brain metabolism [3-5] also occur within the first month of infection. However, difficulties in identifying and studying primary infection in human subjects have thus far precluded these results from being verified. We now report the validation of metabolism changes in the brain early during HIV infection, and the correlation of NAA levels with the expansion of a specific monocyte subset believed to traffic HIV into the brain.

Methods: Six subjects with primary/early HIV infection and eight healthy controls underwent ^{1}H MRI and MR spectroscopy (MRS) at 1.5 T (GE Signa LX scanner) using a standard clinical GE head coil. Single voxel spectroscopy was performed using standard clinical parameters (TE/TR 35/3000 ms, voxel size 20 x 20 x 15 mm^3, 128 acquisitions, 2048 data points) and a voxel was placed on the midline of the frontal cortex. Data were acquired with the GE pulse sequence PROBE-P, a PRESS sequence with CHESS water suppression. HIV subjects were imaged within 60 days of an indeterminate/positive western blot, and while they still had detectable viral RNA levels (on average, 10^5 copies/mL). Subjects had blood drawn within 48 hours of imaging for immunologic analysis with RT PCR to determine viral load and flow cytometric sorting of T cell and CD14/CD16 monocyte subsets. Spectra from the frontal cortex were analyzed using LCModel software [5] to determine absolute concentrations and ratios for the following metabolites: N-acetylaspartate (NAA, includes NAAG), choline (Cho), myo-inositol (MI), glutamate + glutamine (Glx), and creatine (Cr). Differences between cohorts were analyzed by two-tailed *t* tests and linear correlations between metabolic and immunologic factors were found.

Results: In the frontal cortex, subjects with primary HIV infection had lower levels of Cho/Cr (15% lower, $p < 0.03$), absolute Cho (11% lower, $p < 0.03$), NAA (14% lower, $p = 0.01$), and Glx (14% lower, $p < 0.01$) than healthy controls (Figure 1). MI and Cr in the frontal cortex were not significantly different between the two groups at this stage of infection. HIV subjects also demonstrated a lower proportion of CD4+ T lymphocytes ($p < 0.005$) and a higher proportion of CD8+ T lymphocytes ($p = 0.0002$) and monocytes ($p < 0.07$) in their blood. Lower NAA levels were correlated with this difference in CD8+ T cells ($R = -0.57$, $p = 0.05$), specifically with a reduction of naïve CD8+ cells ($R = 0.67$, $p < 0.05$) and a proliferation of effector CD8+ cells ($R = -0.80$, $p = 0.01$). NAA levels were also correlated with an expansion of CD14^{low}CD16^{high} monocytes ($R = -0.73$, $p < 0.02$) (Figure 2).

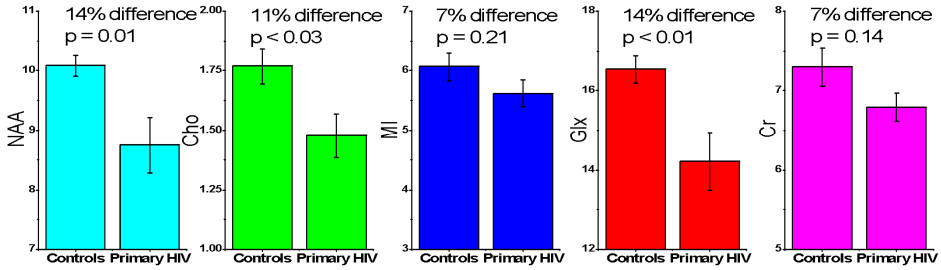

Figure 1. Differences in metabolite levels between subjects with primary HIV infection and healthy controls, measured by ^{1}H MRS in the frontal cortex.

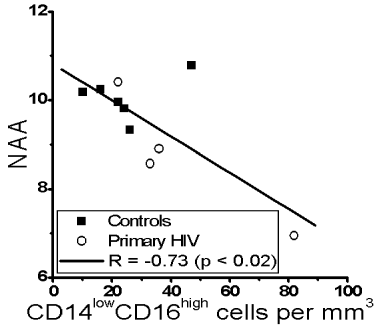

Figure 2. Lower levels of NAA, a neuronal marker, correlate with an expansion of CD14^{low}CD16^{high} monocytes.

Conclusion: These results verify that metabolism changes are occurring in the brain early during HIV infection. Choline decreases have rarely been reported in neurologic diseases, but we have confirmed the early Cho/Cr decreases as found in SIV infected macaques after peak viremia. Lower NAA and Glx levels suggest that HIV causes neuronal injury not only in the chronic stage of infection, but soon after viral entry. Neuronal injury correlates with an expansion of monocytes, especially the CD16+ subset, which may already be bringing HIV into the brain and establishing a viral reservoir at this early stage. Neuronal marker NAA changes with CD8+ T cells at this timepoint, but no correlation with CD4+ T cells (as seen in chronic stages of HIV-associated dementia) was found. Utilizing ^{1}H MRS to track NAA levels may provide important information on brain metabolic health while monitoring immunologic markers in the periphery and targeting CD16+ monocytes with drug therapy.

References

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