Metabolism Reflects Progressive HIV-1 Associated Neuropathology in Humanized Mice

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• **TARGET AUDIENCE –** Scientists interested in the pathobiology of HIV-1 induced brain dysfunction.

• **PURPOSE –** The effects of peripheral HIV-1 infection in humanized mice include brain pathology which, in part, reflects human disease. Here, we determined relationships between neuropathology and brain metabolites with the intent to develop useful biomarkers for the diagnosis and therapeutic monitoring of neuroAIDS progression.

• **METHODS –** Humanized NOD/*scid*-IL-2Rg$_c^{null}$ mice transplanted at birth with human CD34$^+$ hematopoietic stem cells were infected with HIV-1$_{ADA}$ at 22 weeks of age and followed for 16 weeks. Animals were scanned using PRESS ^{1}H MRS in the cortex with NA=576, TR=4000 ms, TE = 50 ms at 16 weeks post infection to measure metabolite concentrations. Spectra were analyzed using QUEST in jMRUI and normalized to percent total metabolite signal. Following spectroscopic examination, mice were sacrificed and brains were analyzed immunohistochemically for neuronal, oligodendrocyte and glial inflammatory markers. Correlations between quantitative immunohistochemistry (fluorescent counts/μm^2) and metabolite levels (percent total metabolite levels, institutional units) were determined using Spearman correlations with exact p-values.

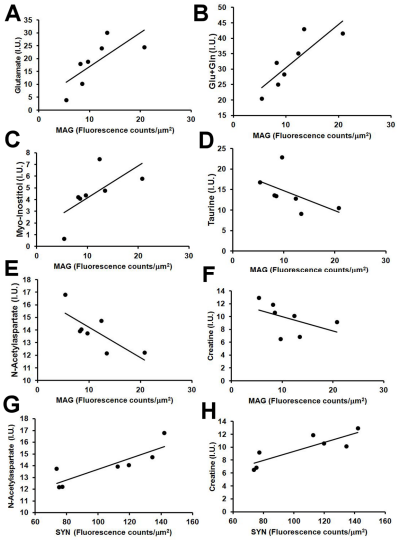

Figure 1. *Correlations between cortical metabolite concentrations and quantitiative fluorescent immunohistology.*

• **RESULTS –** Mice showed sustained plasma viremia with concomitant reductions in CD4$^+$ T lymphocytes. Systemic viral loads were associated with selective cortical N-acetylaspartate, creatine and choline reductions. Post-mortem multispectral imaging microscopic analysis of brain tissue showed reductions in myelin associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), and synaptophysin (SYN), with increased microtubule-associated protein 2 (MAP2) and Glial fibrillary acidic protein (GFAP) after 16 weeks HIV-1 infection (data not shown). Significant correlations were found between reduced MAG in the M2 region of the cerebral cortex and concentrations of the metabolites glutamate (Fig1 1A, r=0.929, p=0.024), glutamate + glutamine (Fig 1B, r=0.857, p=0.006), myoinostitol (Fig 1C, r=0.857, p=0.024) as well as a trend for increased taurine (Fig 1D, r=-0.750, p=0.066). In addition, there was a trend for increased N-acetylaspartate (Fig 1E, r=-0.714, p=0.088) and creatine (Fig 1F, r=-0.750, p=0.066) with reduced MAG. Similar, but opposite relationships existed between synaptophysin and N-acetylaspartate (Fig 1G, r=0.893, p=0.012), and creatine (Fig 1H, r=0.857, p=0.024).

• **DISCUSSION –** MAG reduction indicates reduced metabolism of the oligodendrocytes, a feature of the human disease[1]. Association of oligodendrocyte dysfunction with increases in NAA is expected[2] and likely a confounding factor in the discordance of results from HIV-1 positive patients. This provides an overall picture of cortical metabolism changes from HIV-1 infection showing that processes leading to synaptic loss are associated with loss of NAA and creatine, while reduced MAG is associated with increases in NAA, creatine, taurine, and reductions in glutamate and myoinostitol.

• **CONCLUSION –** These results demonstrate, for the first time, relationships between neuropathology and ^{1}H MRS findings in the cortex of virus-infected humanized mice. Development of such biomarkers reflective of human infection can be applied to novel therapies being developed in our laboratories and elsewhere.

• **REFERENCES** – 1. Dousset V, Armand JP, Huot P, Viaud B, Caille JM. Magnetization transfer imaging in AIDS-related brain diseases. *Neuroimaging Clin N Am*. 1997;7(3):447-460.

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