NAA factor scores suggest neuronal recovery during antiretroviral therapy: an MRSI study

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Introduction: While the frank dementia once seen in patients dying of AIDS has subsided due to the success of antiretroviral therapy (ART), increased patient survival has increased the prevalence of moderate, protracted forms of HIV-associated cognitive impairment (HACI) [1]. Longitudinal magnetic resonance and cognition studies are lacking with respect to the effects of anti-retroviral therapy (ART) use in chronically HIV-infected subjects, especially those with HACI. The few reports that do exist typically focus on changes which occur during the first 3 months of infection [2, 3]. Factor analysis of magnetic resonance spectroscopic imaging (MRSI) data from a cross-sectional study of a chronically infected cohort was found to be able to distinguish between those infected with HIV (a "choline factor") and those with cognitive impairment (an "NAA factor") [4]. In this study, chronically infected HIV+ subjects underwent serial MRSI and cognitive testing at baseline, 3 and 10 months after initiating a new ART regime. The aims were to determine 1) if MRSI factors could detect an improvement in brain metabolism after the initiation of a new anti-retroviral regimen and 2) the longitudinal effects of ART on cognition over 10 months of therapy.

Methods: Fifty-one chronically infected HIV+ subjects underwent MRSI before initiating a new ART regimen, and at 3 and 10 months thereafter. Most subjects were not anti-retroviral naïve, but were either failing or not adhering to their current regimen, thus requiring initiation of new ART. MRSI used a multi-slice spin-echo sequence (TE 280 msec) with two-dimensional phase-encoding, water suppression, and outer-volume lipid suppression. Three 15-mm thick slices (2.5 mm gap) were recorded with the lowest slice placed at the level of the 3rd ventricle. N-acetyl aspartate (NAA), choline and creatine concentrations were calculated using the phantom replacement technique in: frontal and parietal white matter, frontal and parietal gray matter, thalamus, basal ganglia, and centrum semiovale. Previous factor analysis of baseline data resulted in the formation of 3 factors: a "choline factor", a "creatine factor", and an "NAA factor" [4]. Choline factor scores (representing choline concentrations in white matter and deep gray matter regions) were able to distinguish between those with HIV infection and healthy subjects, while NAA factor scores (heavily representing NAA in white matter regions) could distinguish subjects with and without cognitive impairment. Within this study, the same factors were used to produce scores for each subject from the 21 MRSI variables collected at each time point. Blood and cerebrospinal fluid (CSF) samples were obtained for viral load quantification and analysis for CD4+ T cells. The severity of dementia in HIV+ subjects was determined by the Memorial Sloan-Kettering (MSK) staging criteria for HIV-associated dementia (25 had MSK $\geq$ 1, and 22 with MSK = 0.5, and 4 with MSK = 0). Subjects also underwent neurocognitive testing covering executive function (Verbal Fluency P, R, W; Trail-Making Test B), verbal memory (Hopkins Verbal Learning Test), informational processing speed (California Computerized Assessment Package), motor speed (Grooved Pegboard, non-dominate), and psychomotor speed (Trail-Making Test A). Repeated-measures (RM) ANOVA were performed to identify significant changes across the three time points, while matched pairs t-tests were used to isolate changes between groups if the RM ANOVA was significant.

Results: Subjects demonstrated signs of a positive response to ART: CD4+ T cell counts were increased after 3 and 10 months (RM ANOVA, $P = 0.0006$), and plasma and CSF viral loads were significantly decreased from baseline values (RM ANOVA: $P = 3.7\text{x}10^{-12}$ and $P = 9.7\text{x}10^{-5}$, respectively). RM ANOVA revealed that the NAA factor scores significantly increased at 3 months and were maintained at 10 months (Figure 1 *left*; $P = 0.0001$). Neither the choline factor nor the creatine factor changed significantly with therapy. MSK scores during this time period did not change ($P = 0.4$). The grooved pegboard non-dominant hand task was the only test to exhibit signs of improvement after therapeutic intervention (RM ANOVA, $P < 0.05$), and did so only after 10 months of therapy ($P = 0.03$).

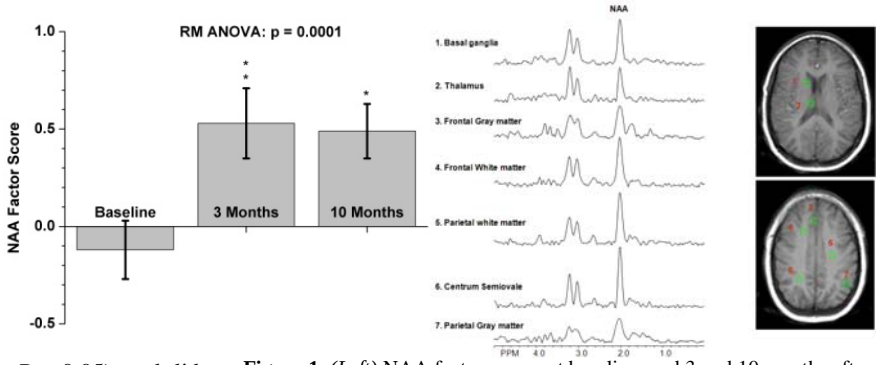

Figure 1. *(Left)* NAA factor scores at baseline, and 3 and 10 months after ART. Error bars are standard error of the mean. * indicates p<0.01, while ** indicates p<0.005 for t-tests between baseline and later measurements. *(Right)* Sample spectra and voxel locations of brain regions analyzed.

Conclusions: The NAA factor (which heavily represents NAA concentrations in white matter regions, and was predictive of dementia at study entry) was found to improve after 3 and 10 months of ART, indicating a reprieve of neuronal dysfunction. This result is consistent with a previous report examining the neuroprotective role of memantine in HACI, which found increased NAA/Cr levels after treatment [5]. However, "glial" metabolism, represented by the choline factor, was not found to change, implying that low-level viral infection, or possibly inflammation/repair mechanisms, may be on-going in the brain after 10 months of therapy. Mathematical models based on immunologic studies indicate that eradication of HIV completely from an infected person, requires treatment for more than 60 years due to latent reservoirs (CD4+ T lymphocytes and mononuclear immune cells) and sanctuary sites (such as the brain) which are impenetrable by many antiretroviral drugs [6, 7]. Interestingly, the lack of MSK and cognitive domain (except fine-motor function) improvement reinforces the idea that recovery of cognitive function is much slower than that of metabolism, perhaps due to persistent low-level infection/inflammation, even after 10 months of ART. It is possible that these cognitive domains recover in a specific manner, but over a longer time period than presently studied.

References:

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Supported in part by NIH R01 MH61438 and K25 NS051129.