Diffuse metabolic abnormalities in acute mild traumatic brain injury: a quantitative proton MR spectroscopy study

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INTRODUCTION: Traumatic brain injury (TBI) classified as 'mild' (mTBI) comprises 85% of cases, ~15% of which involve at least one non-resolving post-concussion syndrome symptom. It is not clear, however, whether the symptomatology is neurological and/or psychosomatic, since conventional imaging is usually unremarkable. Therefore, what distinguishes mild from more severe TBI is the lack of biomarkers to assess injury status and prognosis. While some regions are more prone to TBI injury than others, no single structure has been consistently shown to be involved in mTBI. Quantitative magnetic resonance (MR) techniques detect abnormalities in "normal-appearing" brain, but results are often not reproducible. This suggests that in mTBI, the injury is heterogeneous, diffuse and minimal. Therefore, in this proton MR spectroscopy (^{1}H-MRS) study of acute mTBI, we used a strategy of maximum brain coverage and sensitivity. For comprehensive coverage we used two approaches: (*i*) localized, three-dimensional (3D), ^{1}H-MRS of a large (360 cm^3) volume-of-interest (VOI) of mostly white matter assessing neuronal health, membrane turnover and glial status via their metabolic surrogates *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr) and *myo*-inositol (mI); (*ii*) non-localized, whole-brain NAA (WBNAA) ^{1}H-MRS to cover cortical gray matter and assess global neuronal health. For high sensitivity, all 480 individual spectra from the localized 3D ^{1}H-MRS were frequency-aligned and then summed to yield a single spectrum per subject with excellent spectral resolution and signal-to-noise ratio (SNR).

METHODS: *Subjects:* 14 acute (mean time from TBI 19 days, range 1-54), patients (mean age 35, range 18-56, 3 women) were scanned at 3 Tesla. Three were on medication and 10 reported at least one post-concussion symptom at time of scanning. Nine matched controls (mean age 37, 3 women) were also enrolled. *Localized 3D ^{1}H-MRS:* The $10_{AP}\times8_{LR}\times4.5_{IS}$ = 360 cm^3 VOI was centered on the corpus callosum as shown in **Fig. 1a** and excited with *TE*/*TR* = 35/1800 ms PRESS in 3 sequentially-acquired slabs each with 2nd order Hadamard-encoding in the IS direction. The $16_{AP}\times16_{LR}\times 4.5_{IS}$ cm^3 field-of-view containing the VOI was partitioned into $1.0_{AP}\times1.0_{LR}\times 0.75_{IS}$ = 0.75 cm^3 voxels with $16_{AP}\times16_{LR}$ 2D chemical-shift imaging matrix, yielding 480 nominal voxels. Their spectra were then frequency aligned and summed to yield one global VOI spectrum per subject (**Fig. 1a**). This resulted in: (*i*) $480^{½}$≈22 fold increase in the SNR; (*ii*) superior spectral resolution in comparison to a *single* 360 cm^3 voxel, owing to better B_0 homogeneity across small voxels which is preserved in the sum. Metabolite signals were fitted with the SITools package (1) (**Fig. 1a**) and absolute concentrations were obtained using phantom replacement, incorporating corrections for T_1 and T_2 differences between *in vivo* and *in vitro*. To account for tissue volume variance in the VOI, concentrations were divided by the subject's tissue volume fraction (tissue-volume/VOI-volume) obtained by segmenting MP-RAGE MRI with MIDAS software (2) (**Fig. 1a**). Two-way analysis of covariance (ANCOVA) based on ranks was used to compare patients to controls with respect to each measure, while accounting for the matching of the comparison groups in terms of age and gender. *WBNAA ^{1}H-MRS:* Non-localizing ^{1}H-MRS sequence with *TE*/*TI*/*TR* = 0/940/10,000 ms was used (3). Mean areas of the NAA resonance (**Fig. 1b**) were manually measured by four operators blinded to the subject's identity and the amount of NAA was determined by phantom replacement. This value was divided by the total MIDAS-derived brain volume (**Fig. 1b**) to yield a normalized WBNAA concentration.

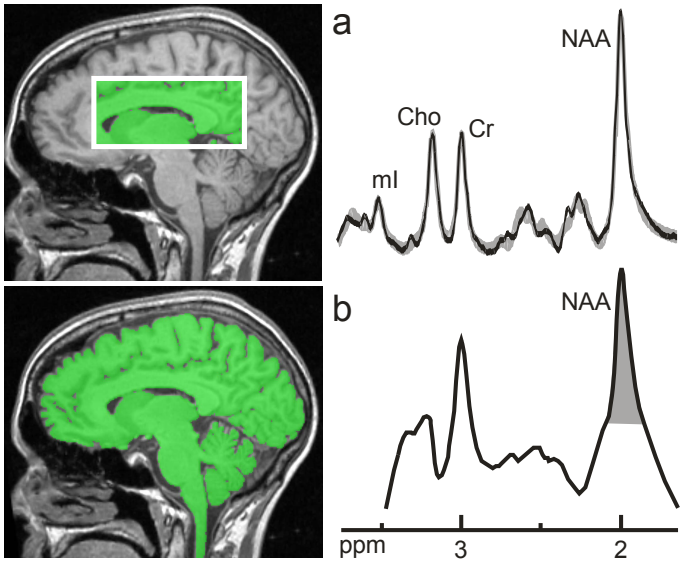

Fig. 1. (**a**) Left: Sagittal T_1-weighted MRI of a patient overlaid with the 360 cm^3 VOI (solid white lines) and its segmentation-derived tissue mask (green). Right: Real part of the ^{1}H spectra sum of all 480 voxels from the VOI in the same patient (black line), superimposed with its fitted model function (gray line) for NAA, Cho, Cr and mI. (**b**) Left: The same image overlaid with its whole brain tissue mask (green). Right: Part of the patient's whole head ^{1}H spectrum. Although several metabolites are seen, only NAA is integrated (uniform gray fill) because it is uniquely localized to the brain.

RESULTS: *VOI:* Patients' average tissue volume fraction (0.94), NAA (7.27 mM) and Cr (5.89 mM) levels were not different (p > 0.2) from controls' (0.94, 7.48 mM, 5.75 mM). In contrast, the Cho and mI concentrations, 1.47, 3.70 mM were 8% and 12% *higher* in the patients versus 1.36 and 3.31 mM in the controls (p = 0.047, 0.031). *Whole brain*: Patients' average brain volume (1162 cc) and WBNAA (11.1 mM) were not different from controls' (1207 cc, 12.2 mM).

CONCLUSION: In the acute stage of mTBI, there is no evidence of brain atrophy, neuronal or axonal damage either globally or diffusely within the 360 cm^3 VOI (normal brain volume, tissue fraction, WBNAA and NAA). Increased Cho and mI suggest diffuse membrane turnover and glial abnormalities in the mostly white matter VOI. Based on the model of diffuse axonal injury (4), these may represent disruptions of cell membrane integrity (Cho) and astroglial scarring (mI) which accompany axonal disconnection.

REFERENCES: 1.Soher, MRM 1998; 2. De Santi, Neurobiol Aging 2001; 3. Gonen, MRM 1998 ; 4. Smith, J Head Trauma Rehabil. 2003.