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

I. Kirov1, J. Babb1, J. Reaume1, R. Grossman1, and O. Gonen1
1Radiology, New York University, New York, NY, United States

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 (1H-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), 1H-MRS of a large (360 cm³) 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) 1H-MRS to cover cortical gray matter and assess global neuronal health. For high sensitivity, all 480 individual spectra from the localized 3D 1H-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 1H-MRS: The 10AP×8LR×4.5IS = 360 cm³ 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 16AP×16LR×4.5IS cm³ field-of-view containing the VOI was partitioned into 1.0AP×1.0LR×0.75IS = 0.75 cm³ voxels with 16AP×16LR 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/ii=22 fold increase in the SNR; (ii) superior spectral resolution in comparison to a single 360 cm³ voxel, owing to better is 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 T1 and T2 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 1H-MRS: Non-localizing 1H-MRS sequence with TE/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.

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 cm³ VOI (normal brain volume, tissue fraction, WBNAA and NAA). Increased Cho and mL 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.