Neuronal Recovery following Traumatic Brain Injury: ^{1}H-MRS Evidence in Humans

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Introduction

Traumatic brain injury (TBI) induces both immediate and progressive brain injury (Chesnut 1993). Secondary axonal damage or reactive change continues for 100 days after TBI suggesting a reversible component (Maxwell 1997). A marker to distinguish between irreversible and potentially reversible brain injury would be valuable in both clinical management of patients with TBI and in the development and evaluation of pharmaceutical agents.

Proton magnetic resonance spectroscopy (^{1}H-MRS) probes signals from N-acetylaspartate (NAA) and total choline (Cho). Cho elevations suggest inflammation, demyelination, or membrane repair. NAA reduction indicates neuronal injury or metabolic depression, and is reduced following TBI (Holshouser 1997). We have shown that brain NAA predicts cognitive functioning and outcome after TBI (Friedman 1999).

Methods

19 TBI and 28 control subjects were examined using MRS and cognitive testing at 1.5, 3, and 7mo following TBI. We used STEAM to sample voxels (25 x 35 x 21mm^3, TE=30ms, TR=2000ms) within normal-appearing posterior white (WM) and gray matter (GM). Relocalization of spectroscopic voxels in follow-up scans was accomplished using previously published methods (Brooks 1999). Time-domain fitting of gaussian lineshapes to NAA, Cre, Cho, mIns and water was by MRUI. Concentrations were corrected for voxel CSF contribution using segmentation of the images from the MRS voxel (Petropoulos 1999).

Cognitive function in domains impaired by TBI: attention and information processing speed; verbal and visual memory; perceptual-motor function; frontal "executive" functioning; pre-morbid intelligence; and orientation, was measured and converted to a mean z-score.

Within individual cognitive and neurometabolite change was determined between 1.5mo & 3mo or 3mo & 7mo. Thus, "cross-sectional" indicates all data collected at a particular exam and "longitudinal" indicates neurometabolite change between two adjacent exams.

Results

Cognitive function increased during each recovery period, especially in the first ($p<0.01$).

Cross-sectional data for WM NAA suggest a rapid fall from normal control values likely associated with irreversible neuronal injury/death and reversible metabolic depression. Similar levels persist at 3 months followed by a small increase at 7 months. Longitudinal data also indicate an NAA increase between 3 and 7 months ($p=0.06$) suggesting recovery from metabolic depression. Cho levels are first elevated at 1.5 months suggesting a reactive response to neuronal injury (inflammation, glial proliferation, edema) but then resolve to the normal range at 3 and 7 months post-TBI.

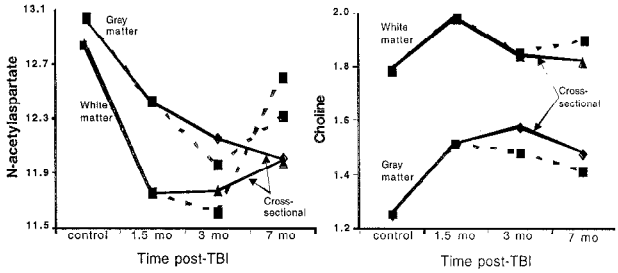

Figure 1 Solid lines indicate all data collected at each time exam (cross-sectional). Dashed lines indicate longitudinal data determined as change from values at 1.5mo post TBI.

Results for GM NAA are similar. As in WM, GM NAA was lower than presumed pre-injury (control) levels by1.5 months post-injury. Although cross-sectional data suggest that this fall continues through 3 and 7 months post-TBI, the longitudinal data suggest a possible small recovery between 3 and 7 months ($p=0.17$), perhaps due to recovery from metabolic depression. Over the same period, GM Cho remains elevated, suggesting continuing removal of dying neurons consistent with findings of macrophages in human brain 240 days after TBI (Gentleman 1999).

Discussion

Longitudinal data reveal increasing NAA possibly indicating neuronal recovery from metabolic depression since the other putative determinant of NAA fall, axonal death, is irreversible. Concurrently, elevated Cho suggests inflammation, glial proliferation, or edema from irreversible neuronal injury. Subsequent falls in Cho indicating resolution of reactive processes, suggests removal of neuronal debris.

We speculate that recovery from metabolic depression is responsible for cognitive recovery following TBI.

Our data suggest that brain injury at the cellular level evolves over an extended period. ^{1}H-MRS offers a new tool to investigate the pathological processes affecting the neuron and may provide new methods for predicting outcome, detecting responders to treatment, and assessing therapeutic intervention.

References

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