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## Proton MR spectroscopy in mild traumatic brain injury

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### Summary

**Background:**

To assess the role of 1H MRS in the detection of changes in cerebral metabolite levels in pyramidal tracts after mild traumatic brain injury (MTBI) and to compare metabolite alterations to the clinical status (Glasgow Coma Scale).

**Material/Methods:**

Study group consisted of 25 patients after mild traumatic brain injury, with a score of 11 to 15 in GCS. The MR studies were performed with a 1.5 T scanner. The results of spectra approximation (presented as metabolite ratios: NAA/Cr, NAA/Cho, Cho/Cr, lac/Cr, lip/Cr, Glx/Cr) were subjected to statistical analysis. MR spectra were recorded from a normal-appearing brain region: internal capsules and cerebral peduncles. Spectra from traumatic patients were compared with a control group including 34 healthy volunteers recorded with the same techniques.

**Results:**

The statistical analysis revealed significant differences between the data obtained from various brain regions of the same patients after an MTBI and between the study and the control group. Proton MR spectroscopy detects changes in cerebral metabolite levels in apparently normal regions. In pyramidal tracts (internal capsules, cerebral peduncles), we noticed a significant reduction of NAA /Cho, lip/Cr, lac/Cr and Glx/Cr.

**Conclusions:**

In patients with mild brain injury, we can detect some metabolite abnormalities in normal-appearing brain structures. Proton MRS is a very useful tool for evaluation of major changes in metabolite levels in pyramidal tracts after mild traumatic brain injury.

**Key words:**

proton spectroscopy • mild brain injury • 1H-MRS

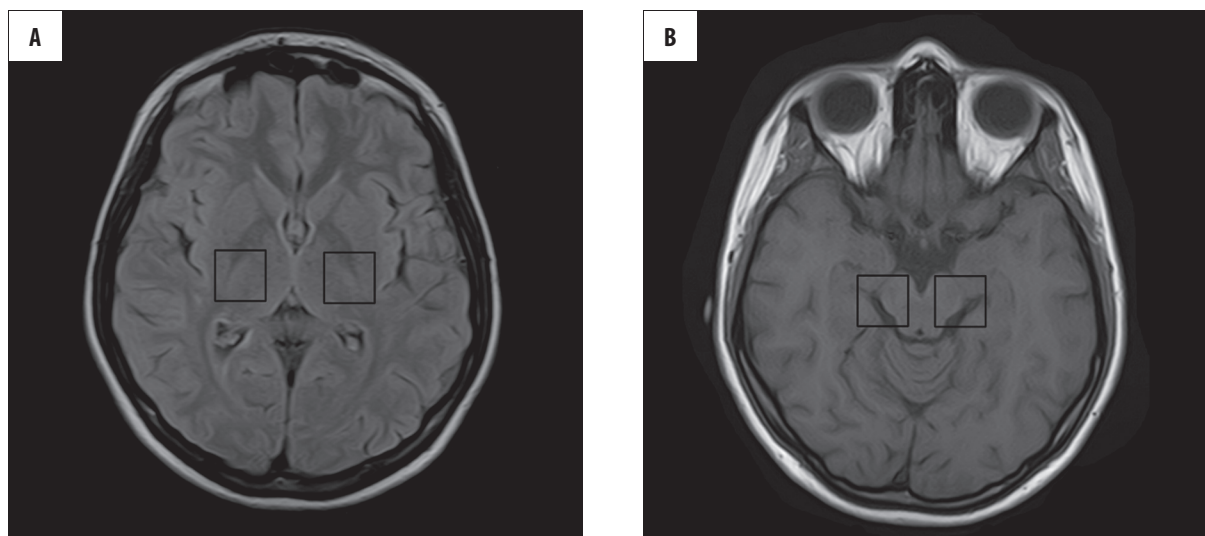
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### Background

Neuroimaging methods, like CT or MR, are very useful in outlining lesions in brain tissue after trauma. However, in mild trauma brain injuries (MTBI), neuroimaging findings are frequently negative. If lesions are observed, they are typically small and few in number. In many cases, the neuroimaging findings do not fully explain the clinical symptoms, and in the absence of any corroborating neuroimaging evidence, these subjects are frequently misclassified. Furthermore, the correlation between early structural neuroimaging findings and long-term clinical outcomes is weak [1]. Diffuse axonal injury is recognized to occur in a

significant number of patients following mild, moderate and severe traumatic brain injury (TBI) [2]. Many injuries tend to be microscopic, producing subtle changes which can be difficult to visualize on conventional imaging (CT or MRI). Consequently, patients may have apparently normal imaging yet remain impaired as a result of a TBI [1]. Although neuroimaging is a central method to define the extent of injury, it is still not sufficient to show the pathophysiological background responsible for all clinical symptoms. Advances in neuroimaging techniques may allow the development of new treatments and refinement of existing therapies aimed at preventing neuronal injury and ultimately improving functional outcome for patients.



**Figure 1.** Localization of voxels of interest in both internal capsules (A) and cerebral peduncles (B).

Proton magnetic resonance spectroscopy ( $^1\text{H}$  MRS) is a safe, non-invasive technique for studying the chemistry of the living brain [3–5].

$^1\text{H}$  MRS studies, which provide *in vivo* measure of neuronal health, are beginning to identify neurochemical abnormalities in mild traumatic brain injury.  $^1\text{H}$ -MRS can be used to quantify a range of brain metabolites, including *N*-acetylaspartate (NAA), a marker of neuronal density and/or mitochondrial function; choline-containing compounds (Cho), a measure of membrane synthesis/turnover; creatine and phosphocreatine (Cr+PCr), a measure of cellular energy metabolism; and *myo*-inositol, a major osmolyte and precursor to several brain metabolites [6–11].

The objective of this study was to demonstrate whether  $^1\text{H}$  MRS could be a useful tool for detecting a microscopic axonal injury after a mild traumatic brain injury.

## Material and Methods

The study group included 25 patients (16 men, 9 women) after mild traumatic brain injury, with a score of 11 to 15 in Glasgow Coma Scale. Their mean age was 43 years (range 22–75). MR imaging and  $^1\text{H}$  MR spectroscopic imaging ( $^1\text{H}$  MRS) data were collected for 1–20 days (11.3 days on average) after injury. Subjects with other causes of neurologic impairment or diseases known to alter metabolite concentrations, as well as patients with a history of a serious head injury were excluded. Spectra from traumatic patients were compared with control 34 healthy volunteers recorded with the same technique. MRI and  $^1\text{H}$  MRS examination was performed with a 1.5T Eclipse (Marconi Medical Systems, USA) scanner. Morphological MRI examination of the brain was carried out in transverse planes, parallel to the longitudinal axis of the temporal lobe in SE, FSE and FLAIR sequences, in  $T_1$ - and  $T_2$ -weighted images, and in frontal planes, perpendicular to the longitudinal axis of the temporal lobe, in  $T_1$ -weighted images. The sagittal images were perpendicular to the line connecting the lowest parts of the temporal lobes. Morphological examination enabled us to exclude other pathologies, such as tumors,

infarcts and hydrocephalus, which could have influence on metabolite levels.

$^1\text{H}$  MRS was performed with a single-voxel method. The VOI (volume of interest) was located in the internal capsules and cerebral peduncles, separately on each side (Figure 1).  $^1\text{H}$  MRS examination was carried out with a single-voxel method using PRESS (point-resolved selective spectroscopy) sequence. Routine 3-impulse sequences of 90, 180, 180 degrees and double crusher impulse were used. The examination was preceded with an automated standardization of the field in the entire encephalon/brain (total shimming) and in the examined sample (local shimming). For water suppression, the MOIST technique was used. Spectra were recorded within the following parameters: TE=35 ms, TR=1500 ms, thickness=15 mm, signal averages=192.

Assignment of resonance lines of particular metabolites was based on *N*-acetylaspartate signal with chemical shift set to 2.0 p.p.m. The spectra were analyzed using the manufacturer-supplied software package for the MRS (Marconi). In some cases, it was necessary to correct the phase manually in order to obtain a maximum of symmetrical signal of residual water and to maintain a proper base line.

Relative concentration ratios of particular metabolites, i.e. *N*-acetylaspartate (NAA), choline (Cho), lipids (lip), lactates (lac) and glutamate (Glx) were analyzed in reference to the signal of creatine, considering its level as an inner standard of examination and NAA/Cho ratio. In statistical analysis, we used Wilcoxon test and Pearson's coefficient. The differences were considered statistically significant when  $P < 0.05$ . The Ethics Committee at the Medical University of Białystok in Poland approved the study. Informed consent was obtained from participants' parents.

## Results

We found mild focal hemorrhagic lesions on MRI of 8 patients. Metabolite ratios in the study group were altered,

**Table 1.** Metabolites ratios in the capsula interna and cerebral peduncles in patients with traumatic brain injury (TBI) and control group (X ±Standard Deviation).

| Metabolites        | mTBI group, n=25 | Control group, n=34 | p value |
|--------------------|------------------|---------------------|---------|
| Capsula interna    |                  |                     |         |
| NAA/Cr             | 1.8288±0.437     | 1.8370±0.2651       | NS      |
| NAA/Cho            | 2.07964±0.397    | 1.2741±0.3497       | p<0.001 |
| Lac/Cr             | 0.12157±0.098    | 0.0280±0.027        | p<0.001 |
| Lip/Cr             | 0.4643±0.182     | 1.3541±0.377        | p<0.001 |
| Glx/Cr             | 0.6302±0.143     | 1.0942±0.202        | p<0.001 |
| Cerebral peduncles |                  |                     |         |
| NAA/Cr             | 2.1355±0.491     | 1.8370±0.2651       | NS      |
| NAA/Cho            | 1.8662±0.379     | 1.2741±0.3497       | p<0.001 |
| Lac/Cr             | 0.2170±0.136     | 0.0280±0.027        | p<0.001 |
| Lip/Cr             | 0.7113±1.197     | 1.3541±0.377        | p<0.001 |
| Glx/Cr             | 0.7316±0.181     | 1.0942±0.202        | p<0.001 |

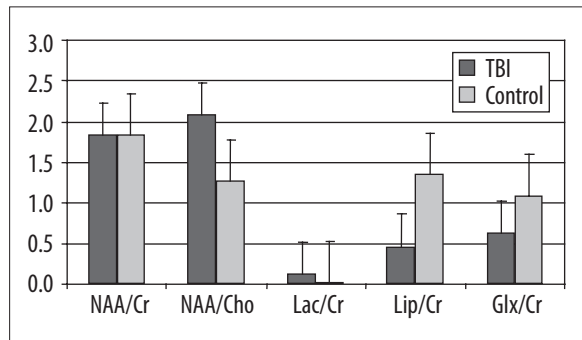
Wilcoxon's test, NS – not significant. NAA – N-acetylaspartate; Cr – creatine; Cho – choline; Glx – glutamate/glutamine.

comparing to the control group. The statistical analysis revealed significant differences between the data obtained from various brain regions of the same patients after MTBI and between the study and the control group (Table 1). Proton MR spectroscopy detected changes in cerebral metabolite levels in apparently normal regions. In pyramidal tracts (internal capsules, cerebral peduncles) we found a significant reduction of NAA /Cho, lip/Cr, lac/Cr, and Glx/Cr (Figures 2, 3). A significant correlation was found between the lip/Cr ratio and the clinical status assessed by Glasgow Coma Scale (R=0.587; P=0.002) (Figure 4).

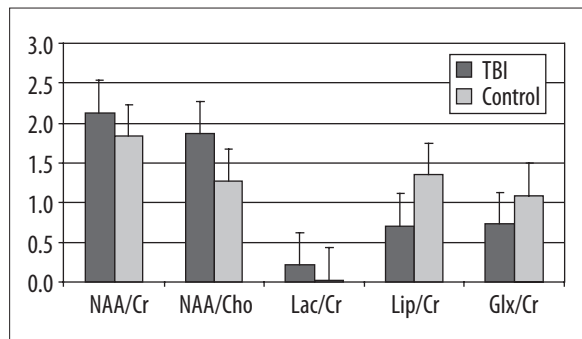
**Discussion**

The primary finding was that the <sup>1</sup>H MRS-identified metabolite ratios were significantly altered in the subacute period following an MTBI, in regions that appeared normal on conventional MR images. This is in keeping with the report by Govindaraju [12]. The patients with MTBI, included in that study, experienced a significant NAA reduction in comparison to their control subjects (Figures 2, 3). Focal lesions visible on MRI were found in only 8 patients out of 25.

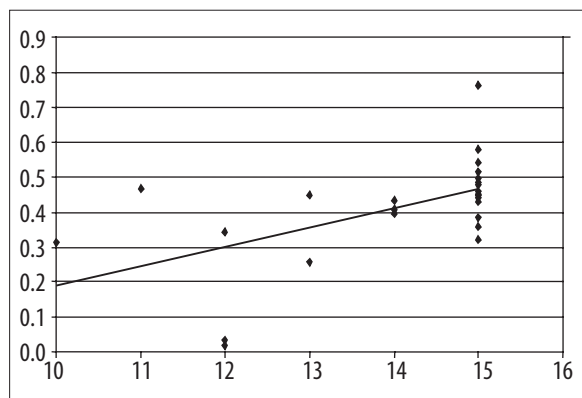
A common finding was the altered metabolite concentrations in the regions that appeared normal on MR imaging; this was indicative of widespread and diffuse tissue damage. This finding included reduced NAA, increased Cho, and increased myo-inositol levels, both in gray and in white matter of such regions as the occipital, parietal, and frontal lobe, and the splenium of the corpus callosum. Increased Lac values were also observed in the acute phase [13,14]. In our study, we observed a higher NAA/Cho ratio, which reflects both an increase of Cho and decrease of NAA.



**Figure 2.** Metabolites ratios in the capsula interna in patients with mild traumatic brain injury (MTBI) and control group (X ±Standard Deviation). Wilcoxon's test, N-acetylaspartate (NAA), creatine (Cr), choline (Cho), glutamate/glutamine (Glx). NAA/Cr TBI vs Control NS; NAA/Cho TBI vs Control p<0.001; Lac/Cr TBI vs Control p<0.001; Lip/Cr TBI vs Control p<0.001; Glx/Cr TBI vs Control p<0.001.



**Figure 3.** Metabolites ratios in the cerebral peduncles in patients with traumatic brain injury (MTBI) and control group (X ±Standard Deviation). Wilcoxon's test, N-acetylaspartate (NAA), creatine (Cr), choline (Cho), glutamate/glutamine (Glx). NAA/Cr TBI vs Control NS; NAA/Cho TBI vs Control p<0.001; Lac/Cr TBI vs Control p<0.001; Lip/Cr TBI vs Control p<0.001; Glx/Cr TBI vs Control p<0.001.



**Figure 4.** Correlation between clinical status (Glasgow Coma Scale) and lip/Cr ratio R=0.587285 p=0.002.

Garnett et al. [15] described a 25% increase in Cho/Cr and a 21% decrease of NAA/Cho in MTBI subjects, compared to controls, and Son et al. [16] reported a 39% reduction in NAA/Cr in pericontusional regions. In a visibly contused brain, the reduction of NAA [17] is likely to be caused by the primary impact, whereas the reduction of NAA in regions of

normal-appearing white matter may reflect a diffuse axonal injury and/or Wallerian degeneration. Diffuse axonal injury occurs in patients after mild, moderate or severe TBI [2]. Most diffuse axonal injuries (DAI) tend to be microscopic, thus producing subtle changes which are distinguishable at post-mortem, but are difficult to visualize on conventional imaging. Alternatively, Wallerian degeneration, the antero-grade loss of axons that connect to regions of focal damage, has been reported to cause loss of NAA in regions of normal-appearing white matter in patients with stroke and multiple sclerosis [18,19]. Cortical contusions or secondary ischemia, both of which are known to occur in patients following TBI, could be the source of the focal injury leading to Wallerian degeneration and hence a reduction in NAA.

In previous <sup>1</sup>H MR spectroscopic studies that examined correlations between altered metabolite levels and injury severity [15,16] or clinical outcome [14,20,21], the common conclusion was that metabolite levels measured within days or weeks after injury are correlated with both initial severity and late clinical outcome. However, these correlations were likely due to the inclusion of subjects with moderate or severe injury. Only few studies have

specifically addressed subjects with mild injury, i.e. the largest group of patients and perhaps the ones most difficult to characterize.

In the present study, we found decreased lac/Cr and lip/Cr ratios in pyramidal tracts. In contrast, in a group of seven subjects, Son et al. [16] found increased Lac/Cr values in edematous areas adjacent to focal contusions visible on T2-weighted MR images. We found only a correlation between the lipid level and the clinical status.

Limitations of this study include a small number of patients, sampling of only a small brain region with a single-voxel <sup>1</sup>H MR spectroscopy, and a limited correlation with outcome evaluations.

## Conclusions

In patients with mild brain injury, it is possible to detect some metabolite abnormalities in normal-appearing brain structures. Proton MRS is a very useful tool for evaluation of major changes in metabolite levels in pyramidal tracts after mild traumatic brain injury.

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