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Original Article

Magnetic resonance spectroscopy abnormalities in traumatic brain injury: A meta-analysis

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ABSTRACT

Background and purpose. – Despite traumatic brain injury (TBI) being common, evaluation with imaging remains challenging. Magnetic resonance spectroscopy (MRS) shows promise in detecting changes of brain metabolite concentrations following TBI; however, currently there are only small studies available without conclusive evidence of the technique's efficacy. The purpose of this systematic review and meta-analysis was to evaluate the association between TBI and MRS metabolite changes.
Materials & methods. – A comprehensive literature search was performed looking for studies reporting brain metabolite concentrations in both TBI and control subjects. Included studies reported values for both adult TBI and control subjects. Cumulative and subgroup meta-analyses were performed using a random effects model.
Results. – The literature search returned an initial 898 manuscripts, of which 36 (which included 748 unique subjects) met study criteria. Cumulatively, NAA/Cr ratios in TBI patients showed a significant decrease as compared to controls (standardized mean deviation [SMD] = −0.88, $P < 0.0001$). When broken into subgroups by severity, the severe and mixed TBI subgroups showed decreases, but the mild TBI (mTBI) subgroup did not. When stratified by time, a significant decrease was seen in the subacute and chronic phases but not the acute phase. Cumulative post-TBI Cho/Cr levels were increased compared to controls (SMD = 0.69, $P = 0.0002$). Significant changes were seen in all subgroups except the mild and mixed mTBI subgroups and the acute phase subgroup.
Conclusion. – Current evidence shows that MRS is able to detect changes to metabolites following TBI, but not in patients with mTBI or in the acute stage.

Introduction

Traumatic brain injury (TBI) is a major cause of morbidity and mortality in the United States [1], with staggering economic costs [2]. Despite the high prevalence and devastating consequences of TBI, clinical diagnosis and prognostication remains challenging. Due to persistent difficulties in accurate classification and neuroimaging assessment, many studies have investigated potentially more sensitive advanced neuroimaging techniques to assess brain injury in the absence of structural damage on conventional structural imaging.

One promising technique for the characterization of TBI is MR spectroscopy (MRS). MRS characterizes brain metabolites using the basic principles of magnetic resonance imaging. The most frequently quantified brain metabolites are N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr), which are respectively theorized to represent markers for neuronal integrity, membrane turnover, and cellular energy [3]. There is a growing interest in metabolites with shorter relaxation times including glutamine, which is released after brain injury as well as myo-Inositol (mIns), a marker of astroglial proliferation. There are many individual studies showing promise in using MRS to detect metabolite abnormalities following

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TBI [4]. However, these studies are predominately small and have conflicting results. To more definitively evaluate this association, we performed a systematic review and meta-analysis to analyze the existing literature to determine whether MRS abnormalities are present in adults after clinically diagnosed TBI.

Materials and methods

We performed this systematic review and meta-analysis following the guidelines of the PRISMA statement [5].

Literature search

A comprehensive literature search was performed by a medical librarian to identify studies that met the following inclusion criteria:

- subjects with clinically defined TBI and control subjects;
- 1H-MRS performed on both cases and controls to quantify metabolites NAA, Cho, Cr, Glx (glutamine and glutamate), or mIns or ratios of metabolites including NAA/Cr, Cho/Cr, Glx/Cr, mIns/Cr.

NAA/Cho ratios were not included due to the small number of studies reporting this ratio. All publication years up to August 2015 were included. Only English language results were included. Because of differences in the brain's response to traumatic injury in adults and children, studies including patients younger than 16 or that had an average patient age under 18 were excluded. Only studies that used closed 1–4 T scanners were included in the meta-analysis. For further search details, please see the Supplement.

Data extraction

The data was extracted from the manuscripts by one study investigator by recording the mean and standard deviation of the metabolites in all ROIs. When studies provided multiple values for a single metabolite, either from multiple ROIs or time points, the values were averaged to provide a single value for the general analyses but kept separate for subgroup analyses. When whole-brain pooled scores were reported along with individual ROIs, the whole-brain scores were used for all analyses except the ROI subgroup analysis. When the mean and standard deviation was not reported, authors were contacted in an attempt to provide the missing information. Additional clinical characteristics of study participants were collected and included the number of subjects; age for both the TBI and control groups; mean or median (median preferred) time from injury to MRS; severity of injury as determined by Glasgow Coma Score (GCS) for the TBI subjects. Studies that did not report GCS scores of the patients but described the injury as a "concussion" were assumed to be in the mild TBI (mTBI) category (GCS 13–15). When studies separated subjects into single and multiple concussion subgroups, data from the single concussion group was extracted. Studies were not excluded on the basis of technical parameters including ROI placement and scan parameters.

Subgroup analyses

Three pre-specified subgroup analyses were done:

- studies were stratified based on the severity of TBI based on GCS into groups containing only mTBI patients (GCS 13–15), only severe TBI patients (GCS 3–8), and mixed severities. There were no studies that contained only moderate TBI (GCS 9–12) patients;
- studies were stratified based on time from injury to MRS into acute (first 7 days from injury), subacute (8–90 days from injury) and chronic (> 90 days) subgroups, as defined by the Defense and Veterans Brain Injury Center [6];
- data from individual ROIs across all studies were separated into:
  - thalamus,
  - frontal,
  - temporal,
  - parietal,
  - occipital lobe subgroups for each metabolite.

While there are other regions known to be affected in TBI, such as the genu and splenium, the regional groups were chosen due to availability of published data. Subgroup analysis was not performed when there were fewer than three studies in a subgroup.

Additionally, a post hoc subgroup analysis was done with the metabolites stratified by pulse acquisition sequence (STEAM vs. PRESS). As with the pre-specified subgroup analyses, the post hoc sequence analysis was only done on metabolites which had at least three studies in each subgroup.

Assessment of risk of bias

An assessment of risk of bias of individual studies was performed using four criteria. First, we assessed whether there was age and gender matching of controls with TBI cases. Second, losses to follow-up in studies that reported data at multiple time points were recorded. Third, the metabolites recorded in the methods sections were compared to those reported in the results sections to assess for selective reporting. Fourth, we recorded whether any measures were undertaken to blind investigators to the group status of the participant undergoing MRS.

For each metabolite meta-analysis, the presence of publication bias was evaluated through a funnel plot. The Begg-Mazumdar rank-correlation test was used to assess the presence of publication bias.

Statistical analysis

The studies meeting inclusion criteria were combined in a meta-analysis using a standardized mean difference (SMD) of the metabolite or metabolite ratio between the control and TBI subjects as the summary measure, with an exact 95% confidence interval. Heterogeneity, as measured by I^2, was calculated for all cumulative and subgroup analyses. The data was processed using the R statistical language (Version 3.1.1) using the metafor package (Version 1.5-9). Due to significant study differences between studies in participant characteristics and imaging techniques, a random effects model was used to estimate the overall effect of TBI on metabolite levels in both the cumulative and subgroup analyses. Given the large number of comparisons generated (62 in total), a P-value = 0.0008 (0.05/62) was considered to be a significant difference between TBI and control groups.

Results

Study selection

The literature search returned an initial 898 studies, of which 36 met inclusion criteria (Fig. 1). Reasons for exclusion at the level of abstract screening include animal studies, review/editorial articles, technical guides, retraction due to plagiarism, and foreign language articles. Reasons for exclusion at the level of full-text assessment include re-analysis of previously reported cohorts, inclusion of non-TBI subjects, patients with comorbidities, pediatric patients within cohorts, and using MRS as an outcome for treatment effect. The most common reasons for exclusion were animal studies, review/editorial papers, and studies that mentioned MRS and TBI

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