**Neuropsychological Correlates of Basal Ganglia and Medial Temporal Lobe NAA/Cho Reductions in Traumatic Brain Injury**

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**Background:** Proton magnetic resonance spectroscopy can assess neurochemical sequelae in traumatic brain injury. Metabolic abnormalities are present in the acute or subacute period in patients with traumatic brain injury and correlate with outcome on clinical scales.

**Objective:** To investigate the use of proton magnetic resonance spectroscopy in detecting possible gray subcortical neurochemical impairments and their relationship with neuropsychological performance.

**Design:** Group comparisons and correlations of brain metabolites with clinical and neuropsychological variables.

**Patients and Methods:** Metabolite concentrations were acquired from voxels localized to the basal ganglia and medial temporal region in 20 patients with long-term moderate and severe traumatic brain injury and 20 matched control subjects. Both groups underwent neuropsychological assessment.

**Results:** N-acetylaspartate–choline-containing compounds ratios were decreased in patients in the basal ganglia ($t = -3.28$, $P = .002$) and medial temporal region ($t = -3.52$, $P = .001$). The basal ganglia ratio correlated to measures of speed, motor scanning, and attention.

**Conclusion:** Patients with long-term TBI present a regional correlation pattern that may help identify the neurological basis of cognitive sequelae in traumatic brain injury.

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an absence of focal lesions in the regions of interest on computer tomography, and a normal educational history. The neuroradiologist (N.B.) evaluated patients’ present magnetic resonance imaging (MRI) data. Three patients showed lesions in the prefrontal poles, 4 in the temporal poles, and 1 in both frontal and temporal poles. T2-weighted images showed basal ganglia hyperintensities in 5 patients and hippocampal hyperintensities in 8 patients. Exclusion criteria were abnormal premorbid IQ, aphasia, dysarthria, or motor impairment precluding neuropsychological evaluation. All subjects participated voluntarily; none had a history of TBI or neurological or psychiatric diseases. The local ethical committee approved the study. Signed informed consent was obtained from participants or their parents or guardians. Sample characteristics are listed in Table 1.

**1H-MRS STUDY**

We used a 1.5-T magnetic resonance scanner (Signa 3.0; General Electric, Milwaukee, Wis) to obtain 2 1H-MRS voxels (2 × 2 × 2 cm3), one in the left basal ganglia and the other in the left midtemporal region from a coronal section (Figure). Water-suppressed spectra were acquired using a double-spin, echo point-resolved spectroscopy sequence with a repetition time of 1500 milliseconds and echo times of 114 milliseconds (basal ganglia voxel) and 33 milliseconds (hippocampus voxel). We obtained NAA (at 2.0 ppm) and Cho (at 3.15 ppm) concentrations in 8 patients. Exclusion criteria were abnormal premorbid IQ, aphasia, dysarthria, or motor impairment precluding neuropsychological evaluation. All subjects participated voluntarily; none had a history of TBI or neurological or psychiatric diseases. The local ethical committee approved the study. Signed informed consent was obtained from participants or their parents or guardians. Sample characteristics are listed in Table 1.

**NEUROPSYCHOLOGICAL ASSESSMENT**

The battery neuropsychological tests evaluated frontal and medial temporal lobe functions usually impaired after TBI. To assess memory we used the Rey Auditory Verbal Learning Test, the memory subtests from the Rey Complex Figure Test, and the Warrington Face Recognition Memory Test. Frontal lobe functions were evaluated using the Word Fluency Test (verbal fluency), Continuous Performance Test (attention and information processing speed), Backward Digit Span (working memory), Trail Making Tests (parts A and B) (visual scanning, motor speed, attention, and mental flexibility), Symbol Digit Modalities Test (visual scanning, tracking, and motor speed), and Grooved Pegboard Test (fine motor speed). Global adjustment to activities of daily living and general outcome were assessed using the extended Glasgow Outcome Scale. Neuropsychological tests were administered by a single neuropsychologist (M.A.) blind to clinical and spectroscopic data.

**STATISTICAL ANALYSIS**

All statistical analyses were done using SPSS version 11.0 for Windows (SPSS Inc, Chicago, Ill). The Kolmogorov-Smirnov test showed that all continuous variables had normal distribution. The t test was, therefore, used for independent samples to compare group means in both neuropsychological and MRS variables. The Pearson product moment correlation test was used to correlate spectroscopic metabolites and neuropsychological tests. Since this was an exploratory study, we did not correct for multiple comparisons, but we applied a 2-tailed level of significance of P<.01.

**RESULTS**

As expected, NAA/Cho ratios were significantly lower in both regions in patients with TBI than in controls. Patients with TBIs differed significantly from controls in all neuropsychological tests (Table 2).

The NAA/Cho ratio in basal ganglia correlated with measures of fine motor speed and attention: Backward Digit Span (r=0.63, P=.003), Trail Making Test A (r=0.58, P=.007) (Table 3). In controls, the relationships between neurochemical levels and neuropsychological performance were not significant. For the whole sample of participants, in the hippocampus we found that the NAA/Cho...
Cho ratio achieved significant correlations on the Rey Auditory Verbal Learning Test ($r = 0.40, P = .009$) and on facial memory recognition (the Warrington Face Recognition Memory Test) ($r = 0.50, P = .001$). In basal ganglia, the NAA/Cho ratio correlated with Backward Digit Span ($r = 0.64, P = .00$) and Trail Making Test A ($r = 0.56, P = .00$).

We attempted to relate NAA/Cho concentrations to clinical data, in particular to the presence of hypoxia (minimum cerebral perfusion pressure), a minimum brain tissue oxygen concentration (PtiO$_2$), and maximum intracranial pressure. We only found a trend toward correlation between the number of local hypoxic episodes (brain tissue oxygen concentration < 15 mm Hg) and the NAA/Cho ratio in the hippocampus ($r = -0.66, P = .02$).

**COMMENT**

Relationships between $^1$H-MRS measurements of metabolic alteration and neuropsychological impairment have been previously reported. We expected correlations between NAA/Cho concentrations and clinical data, in particular to the presence of hypoxia (minimum cerebral perfusion pressure), a minimum brain tissue oxygen concentration (PtiO$_2$), and maximum intracranial pressure. We only found a trend toward correlation between the number of local hypoxic episodes (brain tissue oxygen concentration < 15 mm Hg) and the NAA/Cho ratio in the hippocampus ($r = -0.66, P = .02$).
speed, attention, and working memory. Hippocampal
NAA/Cho ratio correlations were less consistent; we only
found a tendency for visual recognition.

For the whole sample (patients and controls) we ob-
served significant correlations in both NAA/Cho voxels.
The metabolites in the hippocampal region correlated with
memory tests and in the basal ganglia region with frontal
lobe tests. However, these correlations also reflect the
between-group differences in both neuropsychological
and spectroscopic findings.

Our voxels focused on gray subcortical structures,
but we cannot guarantee that the NAA level decrease was
not in fact due to the presence of white matter changes.
However, the different correlation patterns observed in
the voxels and their relationship with the functional prop-
erties of the target structures suggest specificity. So voxel
location is a factor in detecting long-term neurological
deficits in TBI. We found that decreases in the basal gan-
glia NAA level reflect neuropsychological sequelae.

Basal ganglia and hippocampus are sensitive to hy-
poxia and ischemia, and the action of excitotoxins on glu-
matate receptors influences the development of acute cen-
tral nervous system injury.11,13 We were unable to relate
the NAA level decrease with clinical data reflecting hy-
poxia or ischemic damage. Further studies with larger
samples are needed to investigate these factors. To con-
clude, our results suggest that abnormal metabolite con-
centrations in basal ganglia are related to frontal lobe
deficits.

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REFERENCES

1. Luyten PR, Den Hollander JA. Observation of metabolites in the human brain by
2. Brooks WM, Friedman SD, Gasparovic C. Magnetic resonance spectroscopy in
3. Friedman SD, Brooks WM, Jung RE, Hart BL, Yeo RA. Proton MR spectroscopic
findings correspond to neuropsychological function in traumatic brain injury. AJNR
4. Friedman SD, Brooks WM, Jung RE, et al. Quantitative proton MRS predicts out-
5. Garnett MR, Blamire AM, Rajagopalan B, Styles P, Cadoux-Hudson TA. Evi-
dence for cellular damage in normal-appearing white matter correlates with in-
jury severity in patients following traumatic brain injury: a magnetic resonance
P. Early proton magnetic resonance spectroscopy in normal-appearing brain cor-
123:2046-2054.
ton MR spectroscopy of brain metabolism changes in vegetative patients. Ne-
MR spectroscopy in the evaluation of axonal injury: correlation with clinical out-
to human traumatic brain injury: a quantitative proton magnetic resonance study.
for detection of axonal injury in the splenium of the corpus callosum of brain-
extracellular neuroactive amino acids in hippocampus after closed head injury
12. Nakano K, Kayahara T, Tsutsui T, Ushiro H. Neural circuits and functional or-
hypoxia-induced membrane depolarization in striatal neurons. Brain. 1996;118:
1027-1038.