Assessment of mitochondrial impairment and cerebral blood flow in severe brain injured patients

Gunes A. Aygok · Anthony Marmarou · Panos P. Fatouros · Birgit Kettenmann · Ross M. Bullock

Abstract

Background We believe that in traumatic brain injury (TBI), the reduction of N-acetyl aspartate (NAA) occurs in the presence of adequate cerebral blood flow (CBF) which would lend support to the concept of mitochondrial impairment. The objective of this study was to test this hypothesis in severely injured patients (GCS 8 or less) by obtaining simultaneous measures of CBF and NAA.

Methods Fourteen patients were studied of which six patients presented as diffuse injury at admission CT, while focal lesions were present in eight patients. CBF using stable xenon method was measured at the same time that NAA was measured by magnetic resonance proton spectroscopy (1HMRS) in the MR suite. Additionally, diffusion weighted imaging (DWI) and maps of the apparent diffusion coefficient (ADC) were assessed.

Findings In diffuse injury, NAA/Cr reduction occurred uniformly throughout the brain where the values of CBF in all patients were well above ischemic threshold. In focal injury, we observed ischemic CBF values in the core of the lesions. However, in areas other than the core, CBF was above ischemic levels and NAA/Cr levels were decreased.

Conclusions Considering the direct link between energy metabolism and NAA synthesis in the mitochondria, this study showed that in the absence of an ischemic insult, reductions in NAA concentration reflects mitochondrial dysfunction.

Keywords N-acetyl aspartate (NAA) · Cerebral blood flow (CBF) · Apparent diffusion coefficient (ADC) · Mitochondrial impairment

Introduction

Traumatic brain injury (TBI) remains a significant clinical entity that may result in death and severe disability among a predominantly young population. Investigators have found that in addition to the structural damage to the brain tissue,
a series of complex pathophysiological mechanisms are initiated by the trauma [9]. These results in less ATP production and disturbance of the ion gradients essential for functional neurons which lead to changes at cellular levels such as swelling in astrocytes and neurons described as cytotoxic edema [8]. Furthermore, glutamate is released and causes a state of excitotoxicity [9] and changes at sub cellular levels such as mitochondrial impairment [7]. Neuronal function ceases, although the neurons may remain viable and recover.

These complex processes involved in energy crisis are not visualized by conventional imaging and one measure of energy crisis secondary to mitochondrial impairment is the amount of NAA reduction which can be measured quantitatively by 1HMRS. NAA is synthesized in mitochondria and found to be almost exclusively located within the nervous system with a concentration which is only second to glutamate [9]. Therefore, NAA reduction is a reflection of mitochondrial impairment and/or neuronal death. However, studies indicate that while 33% of severely head injured patients suffer an ischemic insult in the first 4 h, the proportion of patients with ischemia drops to 5% in the first 24 h [3]. Therefore, we hypothesize that, with an exception of the very first few hours following injury, there is a profound energy crisis even in the presence of adequate CBF. Our objective was to measure NAA and CBF simultaneously and establish the degree to which CBF confounds the interpretation of NAA.

Materials and methods

Patient population and management

After obtaining informed consent, severely head-injured patients with an admission GCS of 8 or less were enrolled. All patients were treated with a standard TBI protocol and received ICP monitoring. Patients were transported to the CT scanner for measurement of CBF by Xenon technique and to the MR suites (Sigma 3.0 T, GE Medical Systems) for measurement of 1HMRS, DWI and ADC and returned to the NICU without complication. All studies were performed within the first two weeks post injury (mean 9 days, range 3–18 days). CBF examinations reported here were performed sequentially on the same day of the 1HMRS and ADC studies.

MRI-1HMRS acquisition technique and data analysis

After stabilization into the magnet, T1 and T2 weighted pulse sequences were used to produce images in the axial and sagittal planes and semi-quantitative analysis of NAA, creatine containing compounds (Cr/PCr), and choline (Cho) was performed using the point resolved spectroscopy (PRESS) pulse sequence (TE=135 ms TR=1500 ms) Following localized shimming and water suppression, a spectrum from 8 cm³ single voxel (SV) was obtained. The NAA, Cho and Cr peak areas were measured and results were reported as ratios. For diffuse injury, six different regions of interest (ROI) were selected including frontal, parietal and occipital lobes. White matter (WM) and gray matter (GM) were identified separately. For focal injury, regions of interest were core, perilesional and the symmetrically corresponding area in the contralateral hemisphere. All these voxels were placed on the white matter regardless of the ROI. Spectroscopy with 3-T magnet has an increased signal to noise ratio that allowed us to obtain spectra with higher resolution. In addition, 3-T magnet reduced the shim time which reduces the time that the patient is away from the neuroscience ICU.

Stable xenon-enhanced CT CBF technique and data analysis

CBF studies were performed using a CT scanner (Siemens, Erlangen, Germany) equipped with Xe-CT CBF imaging (Xe/TC system-2TM, Diversified Diagnostic Products, Inc., Houston, TX). Our technique required the acquisition of four head CT slices, each 10 mm thickness and separated from one another by 5 mm. Two baseline scans were performed at each level followed by multiple enhanced scans during inhalation of 30% xenon and 70% oxygen. CBF maps were calculated by means of the Kety–Schmidt equation using a commercially available package (Diversified Diagnostic Products, Inc., Houston, Texas). ROI’s were positioned on CBF maps which were corresponding to the location and volume of spectral voxel. For purposes of analysis, CBF values below 18 ml/100 g/min were considered ischemic [2].

ADC acquisition technique and data analysis

DWI was performed using SE-EPI sequences. These pulse sequences generated an ADC trace image using a single shot technique with b value of 1,000 s/mm². Twenty five slices were generated with 5 mm slice thickness, 2 mm gap, 26×26 cm FOV, 96×132 matrix.

Statistical analysis

The NAA/Cr, CBF and ADC values were compared with controls for each ROI with an independent t test. Differences were regarded as statistically significant at p<0.05.