Neurometabolites alteration in the acute phase of mild traumatic brain injury (mTBI): an in vivo proton magnetic resonance spectroscopy (1H-MRS) study

Original Investigation

Neurometabolites Alteration in the Acute Phase of Mild Traumatic Brain Injury (mTBI): An In Vivo Proton Magnetic Resonance Spectroscopy (1H-MRS) Study

Vigneswaran Veeramuthu, PhD*, Pohchoo Seow, MSc*, Vairavan Narayanan, FRCS, Jeannie Hisu Ding Wong, PhD, Li Kuo Tan, MEng, Aditya Tri Hernowo, PhD, Norlisah Ramli, FRCR, MBBS

Rationale and Objectives: Magnetic resonance spectroscopy is a noninvasive imaging technique that allows for reliable assessment of microscopic changes in brain cytoarchitecture, neuronal injuries, and neurochemical changes resultant from traumatic insults. We aimed to evaluate the acute alteration of neurometabolites in complicated and uncomplicated mild traumatic brain injury (mTBI) patients in comparison to control subjects using proton magnetic resonance spectroscopy (1H magnetic resonance spectroscopy).

Material and Methods: Forty-eight subjects (23 complicated mTBI [cmTBI] patients, 12 uncomplicated mTBI [umTBI] patients, and 13 controls) underwent magnetic resonance imaging scan with additional single voxel spectroscopy sequence. Magnetic resonance imaging scans for patients were done at an average of 10 hours (standard deviation 4.26) post injury. The single voxel spectroscopy adjacent to side of injury and noninjury regions were analysed to obtain absolute concentrations and ratio relative to creatine of the neurometabolites. One-way analysis of variance was performed to compare neurometabolite concentrations of the three groups, and a correlation study was done between the neurometabolite concentration and Glasgow Coma Scale.

Results: Significant difference was found in ratio of *N*-acetylaspartate to creatine (NAA/Cr + PCr) ($\chi^2(2) = 0.22$, $P < .05$) between the groups. The sum of NAA and *N*-acetylaspartylglutamate (NAAG) also shows significant differences in both the absolute concentration (NAA + NAAG) and ratio to creatine (NAA + NAAG/Cr + PCr) between groups ($\chi^2(2) = 4.03$, $P < .05$and ($\chi^2(2) = 0.79$, $P < .05$)). NAA values were lower in cmTBI and umTBI compared to control group. A moderate weak positive correlation were found between Glasgow Coma Scale with NAA/Cr + PCr ($\rho = 0.36$, $P < .05$ and NAA + NAAG/Cr + PCr ($\rho = 0.45$, $P < .05$)), whereas a moderate correlation was seen with NAA + NAAG ($\rho = 0.38$, $P < .05$).

Conclusion: Neurometabolite alterations were already apparent at onset of both complicated and uncomplicated traumatic brain injury. The ratio of NAA and NAAG has potential to serve as a biomarker reflecting injury severity in a quantifiable manner as it discriminates between the complicated and uncomplicated cases of mTBI.

Key Words: Neurometabolite; mild Traumatic Brain Injury (TBI); Magnetic Resonance Spectroscopy (MRS); *N*-acetylaspartate (NAA); Glasgow Coma Scale (GCS).

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From the Division of Neurosurgery, Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur (V.V., V.N., A.T.H.); Brain and Cognition Recovery Centre, Gleneagles Medini Hospital, Iskandar Puteri, Johor, Malaysia (V.V.); Department of Psychology, University of Reading Malaysia, Persiaran Graduan Kota Ilmu, Educity, Johor, Malaysia (V.V.); Department of Biomedical Imaging, Faculty of Medicine, University of Malaya, Jalan Universiti, 50603, Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia (S.P., J.W.H.D., T.L.K., N.R.); University of Malaya Research Imaging Centre, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia (S.P., J.W.H.D., T.L.K., N.R.). Received November 13, 2017; revised December 18, 2017; accepted January 3, 2018. *Equal first authors (Vigneswaran Veeramuthu & Seow Pohchoo have equal contributions to this manuscript). **Address correspondence to:** N.R. e-mail: norlisahramli@gmail.com

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INTRODUCTION

Deranged metabolites-induced cellular energy crisis is a common occurrence in traumatic head injury (1). The cascading events post trauma may lead to terminal membrane depolarization with excessive release of excitatory neurotransmitters (2), lysis of the cell membranes and apoptosis, disrupting various neural connectivity networks and consequentially affecting neurocognitive function or performance (1). Injury severity in mild traumatic brain injury (mTBI) could be categorized into complicated or

uncomplicated. A complicated mTBI is differentiated from an uncomplicated mTBI by the presence of a closed depressed skull fracture or trauma-related intracranial abnormality or lesion (3,4).

The advent of advanced magnetic resonance imaging (MRI) techniques in recent years have enabled reliable assessment of microscopic changes in brain cytoarchitecture, neuronal injuries, and neurochemical changes resultant from traumatic insults. While conventional computed tomography scans and structural magnetic resonance sequences are usually unable to detect such physiological and biochemical changes occurring at cellular level (5), magnetic resonance spectroscopy (MRS) is capable of evaluating metabolic perturbation associated with mTBI in vivo.

Several MRS studies showed differences between the semiacute, subacute, and chronic stages of mTBI. A study of semiacute mTBI with matched controls found elevated concentrations of glutamate plus glutamine (Gln) signal in the white matter but reduced gray matter (GM) concentrations of Gln at grey matter (GM), 13 days postinjury (6). The reduced GM Gln suggested reduced neural activity. The study also reported elevated WM concentrations of total creatine (Cr), believed to be consistent with an upregulation of WM metabolic activity and ionic balance restoration of high-energy phosphates pool for cellular repair.

Between the early subacute and chronic stage of mTBI, George et al. (2014) reported decreasing trends of thalamic NAA/Cr (*N*-acetylaspartate/creatine) and Cho/Cr (choline/creatine) levels measured in thalamus and centrum semiovale, corresponding with cognitive measures (5), whereas Kierans et al. (2014) found increased putaminal myoinositol (mI), myoinositol/creatine (mI/Cr) and total glutamine/creatine (Gln/Cr) that reflected complex glial and excitatory response to injury in mTBI patients compared to control (7). At chronic stage of 6 months post trauma, decreased NAA/Cr and NAA/Cho in white matter (WM) regions were reported in the parietal lobe and occipital lobe, respectively, together with increased Cho/Cr in the occipital GM (8). There is a scarcity of data on MRS at the acute stage of mTBI, which can, in principle, provide useful information on the very early proton MRS changes. This study aim to investigate the immediate and early neurometabolic changes, in the immediate aftermath of mTBI (10 hours post trauma). Absolute and the more clinically available ratio of metabolites from the brain spectra of patients with complicated mTBI (cmTBI), uncomplicated mTBI (umTBI), and healthy controls were also explored.

METHODS

Participant Recruitment

This prospective study of 48 subjects is composed of 23 cmTBI patients, 12 umTBI patients, and 13 healthy age-matched subjects as the control group. mTBI patients were recruited from the emergency department of the hospital for the duration of 11 consecutive months from April 2013 to March 2014. Informed consent was obtained from the patients and control groups. Local institutional review board (UM/EC. 949.15) ethical approval was obtained for this study. We adopted the Center for Disease Control's (USA) definition of mTBI (9). Mild TBI is generally characterized by one or more of the following: (1) confusion or disorientation, (2) loss of consciousness for less than 30 minutes, (3) transient focal neurological signs, and (4) Glasgow Coma Scale (GCS) of 13–15 upon clinical evaluation. The grouping of injury complexity as complicated (cmTBI) and uncomplicated (umTBI) groups was determined by the presence of intracranial lesion and/or skull fracture, as evaluated by two blinded clinicians, NR (a neuroradiologist) and VN (a neurosurgeon). Patients with a normal brain computed tomography scan (no fracture and no intracranial injury) were classified as umTBI. Details of the inclusion and exclusion criteria of the study are presented in Figure 1.

Age matched healthy controls were recruited on voluntary basis. They were either staff members of the hospital or patients' next of kin. Stringent exclusion criteria as of the patients were used in the recruitment effort.

Magnetic Resonance Imaging Acquisition

MRI scan was performed on cmTBI and umTBI patients upon admission using a 3T MRI scanner (Signa HDx, GE Healthcare, Harvey, IL) with a dedicated 8-channel head coil followed by single voxel spectroscopy (SVS) sequence. The standard imaging protocol and parameters were as follows: (1) axial T1-weighted three-dimensional fast spoiled gradient-recalled echo (FSPGR) with imaging parameters: repetition time (TR) = 6.7 ms, echo time (TE) = minimum 1.9 ms, field of view (FOV) = 31 mm, matrix = 256 × 256, slice thickness = 1.2 mm, slice overlap = 0.6 mm with image scan time of 3 minutes and 48 seconds; and (2) axial T2-weighted fast spin echo (TR = 4240 ms, TE = 102 ms, FOV = 24 mm, matrix = 512 × 384, thickness = 5 mm, spacing = 1.5 mm, and image scan time of 2 minutes and 30 seconds. MRS technique was performed using a point-resolved single-voxel spectroscopy probe-p sequence with the following parameters: TR = 1500 ms, TE = 35 ms, voxel size = 19 × 19 × 19 mm, slice thickness = 20 mm, number of excitation = 128, and scan time of 7 minutes. Axial T1W/T2 weighted were used to position SVS. For cmTBI, SVSs were placed at the white matter adjacent to injury site and the contralateral normal appearing white matter (Fig 2c). For umTBI and control, the SVS were placed in frontal or occipital white matter (Fig 3c and 4c). The SVS placement was carefully placed so as to avoid contact with the subcutaneous fat, skull, vasculature, arachnoid space, and cerebrospinal fluid to mitigate shimming and water suppression effects. Outer volume saturation bands were placed over the MRS volume over anatomy of interest to suppress signal from fat-containing scalp that might contaminate the spectrum. No higher order shimming was used in our study.

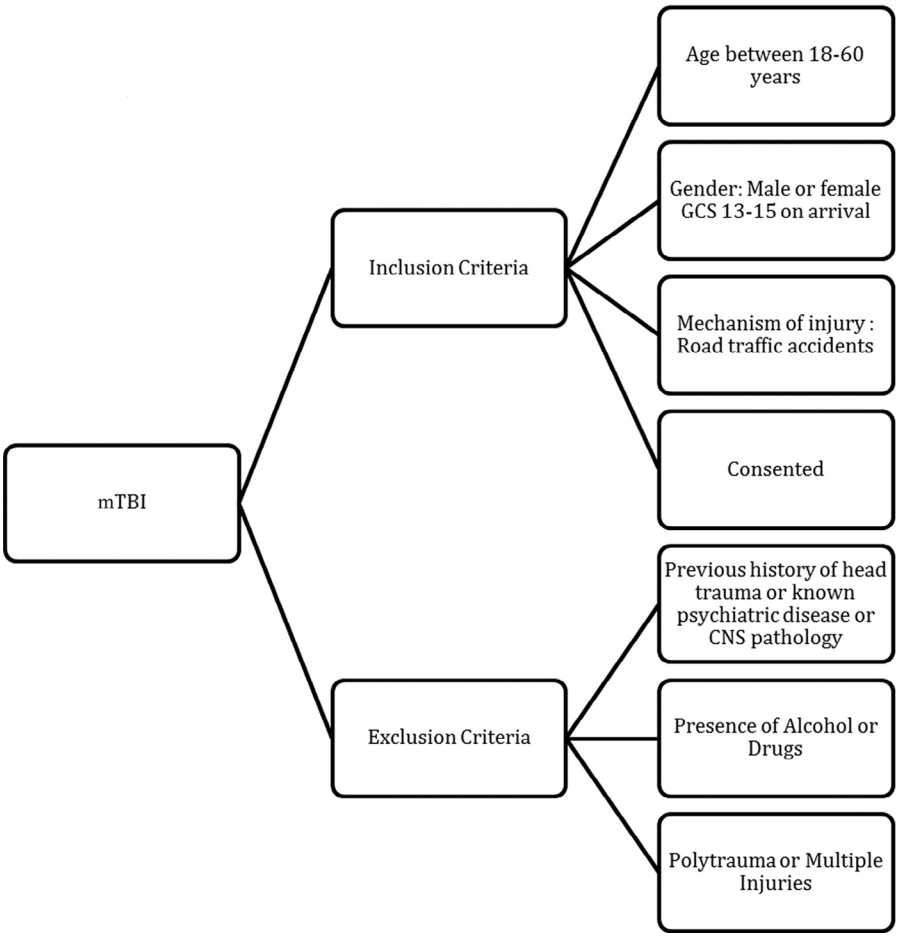

Figure 1. The inclusion and exclusion criteria of the study. CNS, central nervous system; GCS, Glasgow Coma Scale; mTBI, mild traumatic brain injury.

Control participants were subjected to the same MRI protocols as the mTBI patients.

Brain Spectra Analysis

The raw data (P-files) obtained from SVS technique were postprocessed using LCModel (v6.2, LCMODEL Inc., Ontario, Canada) to acquire the brain spectra. Metabolite quantification of the spectra was obtained through spectral fitting from the standard basis set of metabolite solutions in vitro (10). We used the LCModel standard brain spectra setting, which optimizes spectrum fitting for normal brains. The LCModel provides estimation of metabolite quantifications as absolute concentrations (mmol kg^{-1}) and concentration ratio relative to creatine.

Spectra Inclusion Criteria

The quality of spectral curve fitting by LCModel and the reliability of estimated metabolite concentrations were determined using the residuals, full width at half-maximum (FWHM) and Cramér-Rao lower bound (CRLB). The FWHM is an estimate of spectrum line width, which characterizes quality of the in vivo spectrum as a whole. To indicate the quality of fit, CRLB was used to assess the accuracy of metabolites in terms of percentage standard deviations (%SD) of the estimated concentration (11). Lower %SD values indicate that the concentration estimate is more reliable and hence more accurately represent actual concentration (12). Inclusion criteria for spectra data filtering were as follows: (1) acceptable spectroscopy curves from visual inspection (13) of individual metabolite profile performed by a neuroradiologist (NR) who was blinded to the data and diagnosis outcomes of all the subjects; (2) upper limit acceptance of FWHM < 0.1 part per million (ppm) (10); and (3) complying to CRLB criterion where %SD < 20%.

A few of the metabolites are quite difficult to resolve from its counterparts such as choline, NAA, Cr, and Gln (10). They are normally expressed as sums of concentration pairs where the sum of concentrations is much more accurate than the individual concentrations, as reflected in the lower %SD value for the combined metabolite concentrations compared to individual concentration (12).

Statistical Analysis

Statistical analysis was performed using SPSS statistical software version 22 (IBM Corp., Armonk, NY). One-way analysis of variance test was carried out to establish neurometabolic differences among the groups (cmTBI, umTBI, and control)

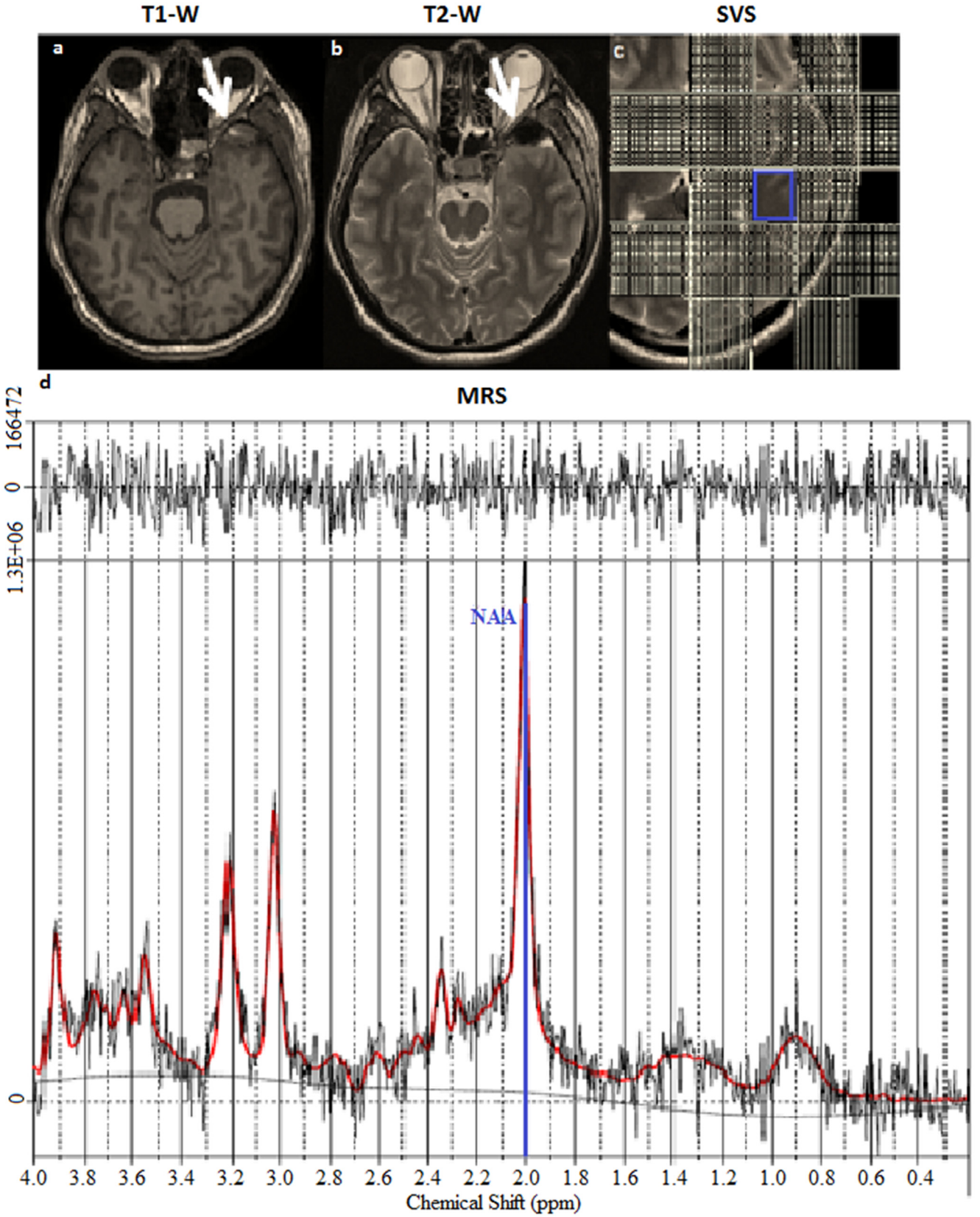

Figure 2. Example of MRI images and spectra of a cmTBI patient with a Lt temporal-extradural hematoma (arrow) **(a)** axial T1-weighted FSPGR, **(b)** axial T2-weighted, **(c)** voxel placed at Lt temporal lobe of white matter (indicated by blue box) with voxel size $19 \times 19 \times 19$ mm, and **(d)** corresponding neurometabolite profiles after preprocessing using LCModel.[10] The red line is the LCModel fit to spectral data. NAA are labeled at the corresponding peaks. The upper plot is the residuals for indication of LCModel fit. cmTBI, complicated mild traumatic brain injury; FSPGR, fast spoiled gradient-recalled echo; MRI; magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; SVS, single voxel spectroscopy. (Color version of figure is available online.)

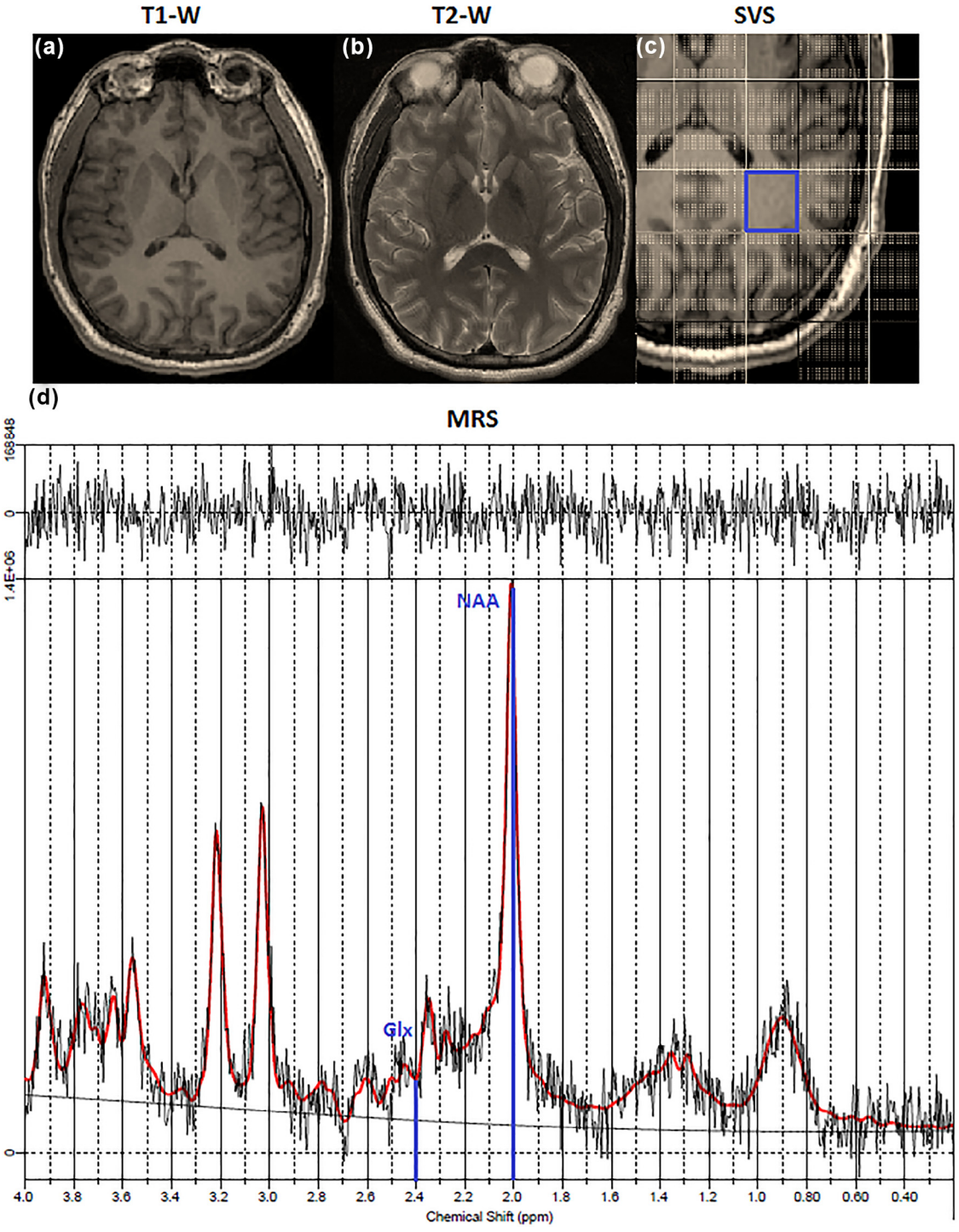

Figure 3. Example of MRI images and spectra of an umTBI patient's **(a)** axial T1-weighted FSPGR, **(b)** axial T2-weighted, **(c)** voxel placed at Lt occipital lobe of white matter (indicated by blue box) with voxel size $19 \times 19 \times 19$ mm, and **(d)** corresponding neurometabolite profiles after preprocessing using LCModel.[10] The red line is the LCModel fit to spectral data. NAA are labeled at the corresponding peaks. The upper plot is the residuals for indication of LCModel fit. FSPGR, fast spoiled gradient-recalled echo; MRI; magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; umTBI, uncomplicated mild traumatic brain injury; SVS, single voxel spectroscopy. (Color version of figure is available online.)

of the absolute concentration and ratio of metabolites. A P value of $< .05$ was declared as statistically significant. Post hoc test was used to determine differences between the groups as a further analysis. Correlations of neurometabolites between the three groups and GCS were determined using Pearson correlation test.

RESULTS

Patient Demography and Clinical Variables

Our study population comprised cmTBI, umTBI, and controls. Clinical variables such as age, years of education, gender, GCS on admission, loss of consciousness, and post traumatic amnesia (PTA) were obtained and tabulated as averages. Table 1 shows the demographic characteristics of mTBI patients and controls. The average MRI scan time for mTBI patients was 10 hours (SD: 4.26) post trauma.

Spectra Analysis

Four spectra were excluded upon visual screening and CRLB criterion, where one spectrum was from cmTBI group, one from umTBI, and two from the control group. A few distinct peaks of metabolite signals were easily measurable. The metabolites were Glu, glycerophosphocholine (GPC), inositol (Ins), NAA, sum of NAA and *N*-acetylaspartylglutamate (NAA + NAAG), sum of creatine and phosphocreatine (Cr + PCr), sum of glutamate and glutamine (Glu + Gln), macromolecules at signals around 0.9 ppm (MM09), macromolecules at signals around 2.0 ppm (MM20), sum mixture of macromolecules and lipids signals at around 0.9 ppm (MM09 + Lip09), and 2.0 ppm (MM20 + Lip20). Figure 2d shows examples of spectra acquired for cmTBI patients.

One-way analysis of variance showed significant differences (in both the absolute concentration and relative ratio over total creatine) for the sum of NAA and NAAG (NAA + NAAG: $\chi^2(2) = 4.03$, $P < .05$ and NAA + NAAG/Cr + PCr: $\chi^2(2) = 0.79$, $P < .05$) and the relative ratio of NAA over total creatine (NAA/Cr + PCr: $\chi^2(2) = 0.22$, $P < .05$) between the three groups (Table 2 and 3). As demonstrated in Figure 2 the NAA peak is lower in cmTBI patients compared to control in Figure 4. Tukey post hoc test revealed that absolute metabolite concentration of NAA + NAAG was statistically lower in cmTBI group compared to control group ($P = .036$) (Table 4). For the metabolite ratio NAA + NAAG/Cr + PCr, significant differences were seen between cmTBI with umTBI ($P = .039$) and control (.007), as shown in Table 5.

Associations Between Neurometabolites With Injury Complexity and GCS

Figure 5 shows the distribution of NAA and its sum across the three groups and GCS scores. The overall concentrations of NAA and its sum were lower in cmTBI compared to the other groups, whereas the sum of NAA and NAAG

TABLE 1. Demographic Information According to Study Groups (cmTBI, umTBI, and Control)

Demographic/Clinical Presentation		Type of Injury		
		cmTBI (n = 23)	umTBI (n = 12)	Control (n = 13)
Age (year)		28.96 (SD 10.2)	28.25 (SD 7.34)	27.15 (SD 4.88)
Education (years)		10.96 (SD 1.97)	12.25 (SD 2.70)	16.31 (SD 3.28)
		%	%	%
Gender	Male	87	83.3	61.5
	Female	13	16.7	38.5
GCS on admission	GCS 13	21.7	0	n/a
	GCS 14	39.1	0	n/a
	GCS 15	39.1	100	n/a
Loss of consciousness	Yes	95.7	83.3	n/a
	No	4.3	16.7	n/a
Post traumatic amnesia	None	21.7	33.3	n/a
	<1 h	52.2	33.3	n/a
	>1 h <24 h	26.1	33.3	n/a
Voxel placement	Frontal lobe	8	2	1
	Parietal lobe	10	8	12
	Temporal lobe	4	0	0
	Occipital lobe	1	2	0

cmTBI, complicated mild traumatic brain injury; GCS, Glasgow Coma Scale; umTBI, uncomplicated mild traumatic brain injury; SD, standard deviation.

TABLE 2. Descriptive Summary for Absolute Metabolite Concentrations

	cmTBI (n = 23) (ppm)		umTBI (n = 12) (ppm)		Control (n = 13) (ppm)		
Metabolites	Mean	SD	Mean	SD	Mean	SD	*P* Values
Glu	2.817	0.387	2.988	0.371	2.736	0.272	.313
GPC	0.572	0.147	0.685	0.068	0.660	0.109	.166
Ins	1.633	0.347	1.759	0.147	1.576	0.271	.878
NAA	2.690	0.536	2.862	0.541	3.019	0.284	.058
GPC + PCh	0.585	0.129	0.666	0.046	0.660	0.109	.076
NAA + NAAG	3.097	0.775	3.235	0.708	3.620	0.352	.027*
Cr + PCr	1.702	0.340	1.693	0.217	1.766	0.225	.591
Glu + Gln	4.195	0.831	4.150	0.422	3.634	0.328	.120
MM09	1.895	0.574	2.20	0.600	2.319	0.477	.173
MM20	3.105	0.826	3.206	0.448	3.614	0.546	.174
MM09 + Lip09	1.98	0.553	2.440	0.354	2.554	0.692	.144
MM20 + Lip20	3.162	0.8	3.215	0.434	3.736	0.608	.264

cmTBI, complicated mild traumatic brain injury; Cr, creatine; Gln, glutamine; Glu, glutamate; GPC, glycerophosphocholine; Ins, inositol; MM09 + Lip09, sum mixture of macromolecules and lipids signals at around 0.9 ppm; MM09, macromolecules at signals around 0.9 ppm; MM20 + Lip20, 2.0 ppm; MM20, macromolecules at signals around 2.0 ppm; NAA, *N*-acetylasparte; NAAG, *N*-acetylaspartylglutamate; PCh, phosphocholine; PCr, phosphocreatine; ppm, parts per million; SD, standard deviation; umTBI, uncomplicated mild traumatic brain injury.
* $P < .05$.

TABLE 3. Descriptive Summary for Relative Metabolite Concentrations Over Total Creatine

	cmTBI (n = 23) (ppm)		umTBI (n = 12) (ppm)		Control (n = 13) (ppm)		
Metabolites (/Cr + PCr)	Mean	SD	Mean	SD	Mean	SD	*P* Values
Glu	1.699	0.293	1.782	0.250	1.567	0.215	.222
GPC	0.343	0.1	0.395	0.035	0.374	0.049	.705
Ins	0.978	0.219	1.050	0.101	0.894	0.129	.291
NAA	1.593	0.202	1.68	0.163	1.72	0.125	.025*
GPC + PCh	0.354	0.097	0.397	0.035	0.374	0.049	.771
NAA + NAAG	1.82	0.282	1.895	0.287	2.059	0.11	.004*
Glu + Gln	2.464	0.435	2.352	0.376	2.051	0.336	.139
MM09	1.098	0.249	1.278	0.253	1.289	0.216	.402
MM20	1.796	0.332	1.882	0.096	2.028	0.361	.282
MM09 + Lip09	1.149	0.229	1.367	0.191	1.418	0.330	.400
MM20 + Lip20	1.831	0.307	1.889	0.099	2.097	0.399	.619

cmTBI, complicated mild traumatic brain injury; Cr, creatine; Gln, glutamine; Glu, glutamate; GPC, glycerophosphocholine; Ins, inositol; MM09 + Lip09, sum mixture of macromolecules and lipids signals at around 0.9 ppm; MM09, macromolecules at signals around 0.9 ppm; MM20 + Lip20, 2.0 ppm; MM20, macromolecules at signals around 2.0 ppm; NAA, *N*-acetylasparte; NAAG, *N*-acetylaspartylglutamate; PCh, phosphocholine; PCr, phosphocreatine; ppm, parts per million; SD, standard deviation; umTBI, uncomplicated mild traumatic brain injury.
* $P < .05$.

TABLE 4. The Post Hoc Test for Absolute Metabolite Concentration NAA + NAAG

					95% CI	
I Group	J Group	Mean Difference (I-J)	Std Error	Sig	Lower Bound	Upper Bound
cmTBI	umTBI	–0.502	0.255	0.132	–1.12	0.116
	Control	–0.636	0.248	0.036*	–1.238	–0.339
umTBI	cmTBI	0.502	0.255	0.259	–0.095	0.459
	Control	–0.134	0.287	0.132	–0.116	1.12

CI, confidence interval; cmTBI, complicated mild traumatic brain injury; NAA, *N*-acetylasparte; NAAG, *N*-acetylaspartylglutamate; umTBI, uncomplicated mild traumatic brain injury.
* Indicates significant difference at $P < .05$.

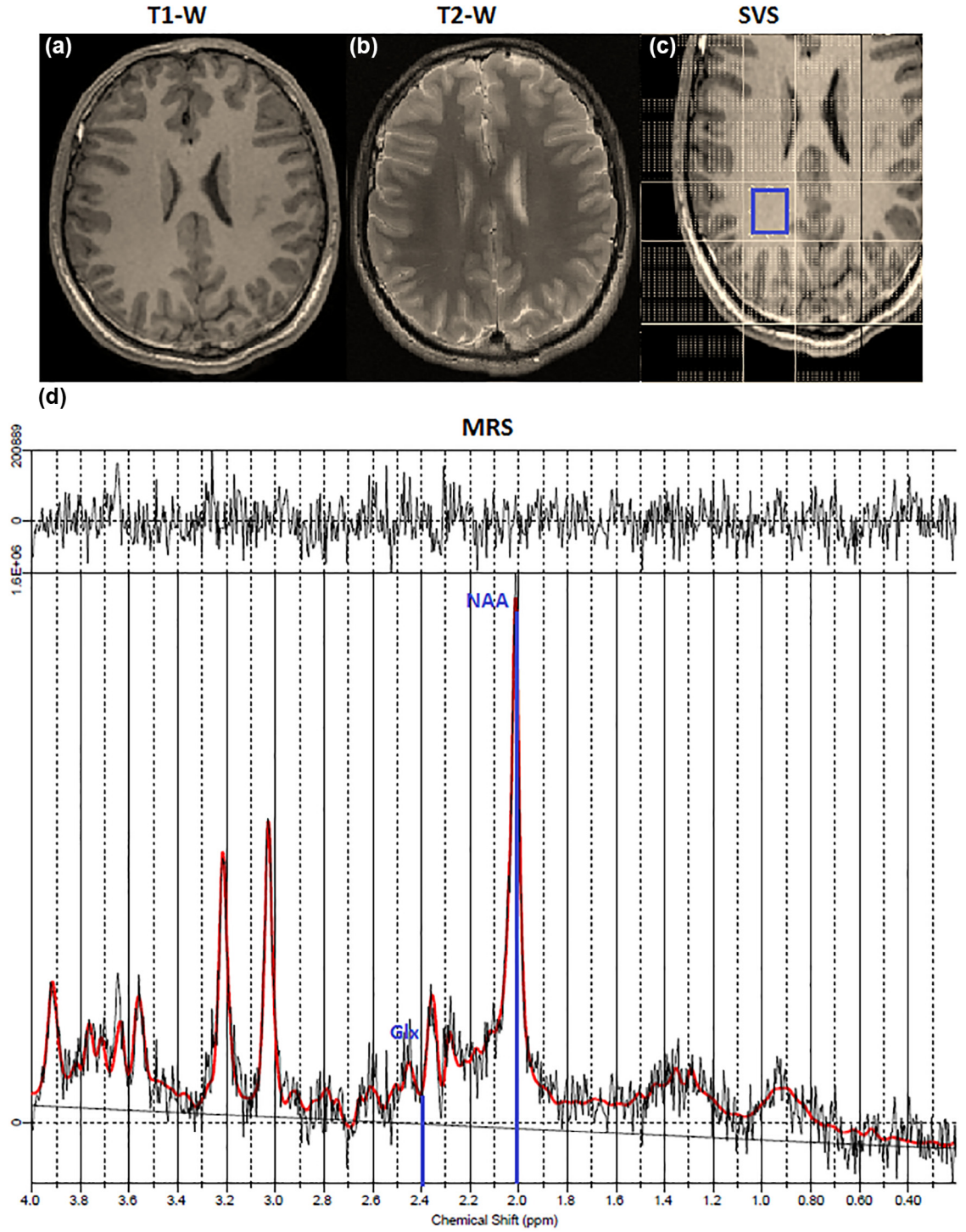

Figure 4. Example of MRI images and spectra of a control patient's **(a)** axial T1-weighted FSPGR, **(b)** axial T2-weighted, **(c)** voxel placed at Rt occipital lobe of white matter (indicated by blue box) with voxel size 19 × 19 × 19 mm, and **(d)** corresponding neurometabolite profiles after preprocessing using LCModel.[10] The red line is the LCModel fit to spectral data. NAA are labeled at the corresponding peaks. The upper plot is the residuals for indication of LCModel fit. FSPGR, fast spoiled gradient-recalled echo; MRI; magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; SVS, single voxel spectroscopy. (Color version of figure is available online.)

TABLE 5. The Post Hoc Test for Metabolite Ratio NAA + NAAG/Cr + PCr

					95% CI	
I Group	J Group	Mean Difference (I-J)	Std Error	Sig	Lower Bound	Upper Bound
cmTBI	umTBI	–0.227	0.899	0.039*	–0.445	0.009
	Control	–0.279	0.088	0.007*	–0.491	–0.066
umTBI	cmTBI	0.227	0.090	0.039*	0.009	0.445
	Control	–0.052	0.101	0.866	–0.297	0.193

CI, confidence interval; cmTBI, complicated mild traumatic brain injury; NAA + NAAG/Cr + PCr, *N*-acetylasparte and *N*-acetylaspartylglutamate/creatine and phosphocreatine; umTBI, uncomplicated mild traumatic brain injury.

* Indicates significant difference at $P < .05$.

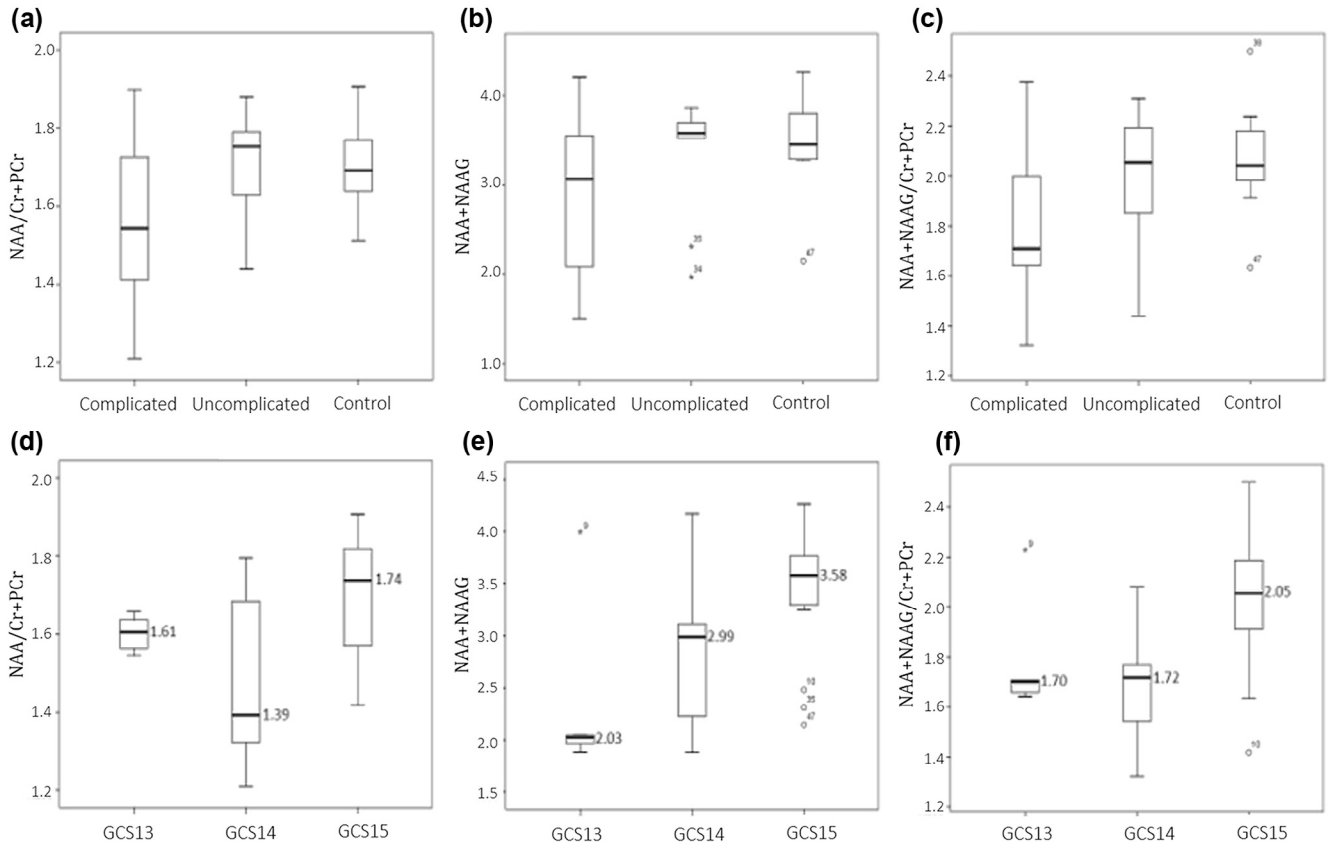

Figure 5. The box plots of neurometabolites distributions **(a)** NAA/Cr + PCr, **(b)** NAA + NAAG, and **(c)** NAA + NAAG/Cr + PCr across the groups, and **(d)** NAA/Cr + PCr, **(e)** NAA + NAAG, and **(f)** NAA + NAAG/Cr + PCr across the GCS scores. The values beside the boxplots describe the median value of the neurometabolites. GCS, Glasgow Coma Scale; NAA/Cr + PCr, *N*-acetylaspartate to creatine and phosphocreatine; NAA + NAAG, *N*-acetylasparte and *N*-acetylaspartylglutamate; NAA + NAAG/Cr + PCr, *N*-acetylasparte and *N*-acetylaspartylglutamate/creatine and phosphocreatine.

showed increasing trend with GCS. A significant weak positive correlation was seen between NAA and its sum with the three groups ($\rho = 0.35$–0.44, $P < .05$). Weak positive correlations were also found between GCS with NAA/Cr + PCr ($\rho = 0.36$, $P < .05$), NAA + NAAG/Cr + PCr ($\rho = 0.45$, $P < .05$), and NAA + NAAG ($\rho = 0.38$, $P < .05$).

DISCUSSION

Spectroscopic evaluation of metabolic profiles could provide valuable information about the degree of neuronal injury as reflected by the changes in neurometabolite concentrations. Hence, in this study, we set out to examine the hyperacute neurometabolic alteration hypothesized to occur in the early hours of a traumatic insult (mTBI) using MRS imaging modality. These mTBI patients generally underwent scanning within an average of 10 hours post trauma to minimize possible confounding factors such as ongoing secondary damage or recovery mechanisms. Secondary injuries like diffuse axonal injury, inflammation, edema, apoptosis, excitotoxicity, and mitochondrial dysfunction can cause fluctuations in the metabolite profiles at a later stage of brain injury (5). We found that

neurometabolite alterations were already apparent at this early phase. Previous studies in this field has revealed microstructural changes which occur within hours after the initial insult affecting WM integrity, resulting in neuropsychological impairments (14).

The absolute metabolite concentrations of total NAA and NAAG and ratio metabolite concentrations of NAA and its counterpart over creatine (NAA/Cr + PCr and NAA + NAAG/Cr + PCr) showed statistically significant changes in this study. The NAA and its related compound, NAAG also demonstrated statistically significant difference among the patients with cmTBI in comparison to the healthy controls. Additionally, we also found that the spread of NAA values were wider in cmTBI group (Fig 5), suggesting possible disease heterogeneity among patients with mTBI. NAA is believed to be the source of metabolic acetate for oligodendrocyte myelination and serves as a precursor for the synthesis of the neurotransmitter NAAG (15). Levels of NAA and NAAG are dysregulated in various disease states associated with aberrant oligodendrocyte differentiation. Traumatic insult to the brain, however, induces the disturbance of neuronal integrity that results in mitochondrial dysfunction and NAA synthesis perturbation (1,5).Various studies have reported that the depression of NAA and NAAG levels due to neurometabolic impairment in concussed subjects is a common occurrence (16–18).

The NAA also serves as an osmolyte in neuronal tissues and a source of acetate for myelin synthesis in the glial cells, a process that is usually disrupted in the aftermath of a traumatic insult (19). The sudden decrease or reduction in NAAG concentration thereafter causes a sudden surge in glutamate generation that consequentially leads to mitochondrial dysfunction (18), affecting the neuronal homeostasis and viability. Hence, the significant downward trend of NAA in cmTBI and its association with clinical markers such as the GCS scores as seen in our study cannot understate the importance of NAA as a parameter for brain injury detection. Although the complete pathophysiology of NAA reduction and altered level of consciousness post trauma is not readily known, its viability as a marker has been established and is possibly attributed to substantial cellular (neuronal/axonal) injury in patients with mTBI (6,20). Hence, the importance of early measurement of NAA levels post trauma (less than 48 hours) has been consistently noted as a good marker for disease severity classification and prognostication, and cannot be ignored for long (6,21–23).

The major limitation of our study is the small sample size especially in the umTBI group in comparison to the cmTBI group. Heterogeneity of location may confound interpretation of the spectroscopy, as metabolite ratios are known to vary from brain region to brain region. Our study did not take into account the widespread global effect of tissue damage on the entire brain parenchyma because of limitation of placement of ROI (region of interest) in the SVS. A longer follow-up data would be necessary to establish the usefulness of NAA for diagnosis and prognosis of mTBI.

CONCLUSION

A decline in NAA and NAAG ratio was associated with decreasing injury severity (based on GCS), at the acute stage of an evolving brain injury in mTBI. This study revealed the potential application of NAA and NAAG as a biomarker to discriminate between the mTBI subgroups (complicated and uncomplicated cases) in a more quantifiable manner. The knowledge of early onset neurometabolite alterations and its correlations with injury severity adds another degree of intricacy to the understanding of mTBI mechanism. Future work in this area should explore the neurometabolic changes in all injury severities (ie, mild, moderate, and severe head injury).

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