ORIGINAL RESEARCH PAPER

Volume-7 | Issue-11 | November-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CORRELATION OF 1H MR SPECTROSCOPY METABOLITES LEVEL IN BILATERAL BASAL GANGLIA WITH CLINICAL STATUS AND OUTCOME IN PATIENTS OF MILD AND MODERATE TRAUMATIC BRAIN INJURY

Neurosurgery

Dr Verma Siddharth — Senior resident, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi

Dr Shankar KB* — Mch, Professor and Head, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi *Corresponding Author

Dr Sharma KC — Mch,Professor in the Department of Neurosurgery Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi

ABSTRACT

Traumatic brain injury(TBI) is one of the major causes of morbidity and mortality. MR Spectroscopy provides a measure of cerebral metabolite levels. **METHODS:** A total of 45 patients with mild to moderate TBI were included over the period of 17months. Ratios of NAA/Cr, Cho/Cr & NAA/Cho (metabolites level) were correlated with clinical status (using Glasgow Coma Scale) and outcome after 3 months (using Glasgow Outcome Score) at B/L basal ganglia level.

RESULTS In our study patients age ranged from 20 to 60 years. ^{1}H MR spectroscopy was performed during sub acute period (mean 7-15 days). Metabolite ratios of NAA/Cr, Cho/Cr & NAA/Cho at bilateral basal ganglia did not show any correlation with Glasgow coma scale ($p=0.61$,$p=0.18$,$p=0.24$ respectively) however, statistically significant correlation exists with Glasgow Outcome Score ($p<0.0001$). **CONCLUSION:** 1H MR spectroscopy of bilateral basal ganglia did not show any correlation with clinical status but significant correlation exists with Glasgow Outcome Score (GOS).

KEYWORDS

Glasgow Coma Scale (GCS), Glasgow Outcome Score (GOS) , 1H MR spectroscopy(MRS), N-Acetyl Aspartate (NAA), choline-containing compounds (Cho), Creatine (Cr)

INTRODUCTION

Traumatic brain injury is one of the major causes of morbidity and mortality. Globally it is estimated that the annual incidence and mortality from Traumatic Brain Injuries (TBI) is 200 and 20 per 1, 00,000 per year, respectively.[1] Brain injuries are classified into mild, moderate and severe categories. [2] The Glasgow Coma Scale (GCS), the most commonly used system for classifying TBI severity, grades a person's level of consciousness, based on verbal, motor, and eye-opening reactions to stimuli. TBI with a GCS of 13 or above is mild, 9–12 is moderate and 8 or below is severe. [3, 4] TBI can be focal or diffuse. [5]

Radiological imagings like CT scan and Magnetic Resonance Imaging are very useful tools in out lining lesions in brain after injury.[6] However, in many cases, these imagings do not correlate with clinical status and outcome of the patient. In mild injuries, these imagings are frequently normal or show subtle changes. Diffuse axonal injuries can occur after mild, moderate or severe head trauma but conventional imagings do not depict it. Further, many injuries are microscopic which cannot be visualized by conventional imaging.[7,8]

MR Spectroscopy provides a measure of cerebral metabolite levels. The nuclei which are commonly used in MRS are ^{1}H (Proton), ^{23}Na (Sodium) and ^{31}P (Phosphorus). Proton Spectroscopy has benefits that, it is easy to perform, provide more signal to noise, less time consuming (10-15 minutes). ^{1}H MRS provides in vivo evidence of microscopic injury.[9] ^{1}H-MRS can be used to measure a range of brain metabolites, including N-Acetyl Aspartate (NAA), a marker of neuronal function; choline-containing compounds (Cho), a measure of membrane synthesis; Creatine and Phosphocreatine (Cr+PCr), a measure of cellular energy metabolism; and myo-Inositol, a major osmolite and precursor to several brain metabolites.[10-13]

MRS is not used routinely in acute head injuries. Conventional techniques like CT and MRI are used routinely and they demonstrate pathologies like fractures and intracranial hemorrhages that require urgent neurosurgical interventions, but these imagings frequently don't correlate with clinical conditions and outcome of the patients. So an alternate method is required to correctly explain the condition of head injury victim & to predict the prognosis of patient.

^{1}H MR Spectroscopy metabolic alterations have been detected in patients with TBI and correlated with status and outcome[10,11,13] In previous studies, MR Spectroscopy voxels have been placed in different regions of brain.[11-14] Basal ganglia is sensitive to hypoxic, ischemic, metabolic & molecular events in TBI and generally not involved by direct trauma.[14] The pertinent question therefore is whether metabolite level/ratio at basal ganglia level detected by ^{1}H MRS can explain the clinical status (using GCS) and outcome (using Glasgow Outcome Scale) of the patients.

MATERIALS & METHODS: This was a prospective study conducted in Department of Neurosurgery, Safdarjung Hospital and Vardhman Mahavir Medical College, New Delhi. A total of 45 patients with mild to moderate TBI who fulfilled the inclusion and exclusion criteria were included after taking their consent over the period of 17months. **Inclusion Criteria**1. Age >18 years with the diagnosis of Mild to moderate head injury (GCS), after CT scan/ MRI investigation. Patient giving consent and who were not for emergency neurosurgical intervention. **Exclusion Criteria:** Age < 18 years or > 60yrs. Sever head injury patients with other major chest, abdomen or long bones injuries. Unstable vitals, patients who had visible changes in basal ganglia in CT/MRI. Patients required urgent surgical intervention. Severe co-morbidities (uncontrolled DM, HT, coagulopathies, cyanotic heart diseases, Tuberculosis etc.) Patients with other causes of neurological impairment, major psychiatric illness and history of substance or alcohol abuse. This study was approved from Institutional Ethical Committee.

Patients were classified under mild, moderate & severe TBI as per their post resuscitation GCS. Routine investigations, serum electrolytes, coagulation profile, X ray Chest, ECG and USG abdomen was done to rule out blunt trauma abdomen. NCCT head was done to rule out any operable lesion. In subacute period i.e. once patient became clinically stable, MR imaging and ^{1} H MR spectroscopy of bilateral basal ganglia region was done.

MR spectroscopy technique: 1.5 tesla magnetic resonance scanner was used to obtain ^{1}H-MRS voxels. Voxels (size 2×2×2 cm^{3}) were obtained from right and left basal ganglia. Voxels were placed in the region of globus pallidus and putamen nucleus. Water suppressed spectra were acquired using PRESS with TE=144 ms & TR=1500 ms. Ratios of NAA/Cr, Cho/Cr & NAA/Cho were obtained and correlated with post resuscitation GCS of patient. Patients were followed up, after 3 months outcome was measured on the basis of Glasgow Outcome Scale(1-5score) and correlated with ratios of NAA/Cr, Cho/Cr & NAA/Cho.

Glasgow Outcome Scale was further divided in to two groups. GOS of 5 was taken as Good recovery and 1-4 score as Less than good recovery

STATISTICALANALYSIS

The data was analyzed using Graph Pad Prism version 5.00 for Windows (Graph Pad Software, Inc., USA). P value of < 0.05 was considered as statistically significant (Confidence interval of 95% was taken into account).

RESULTS: A Total of 45 patients with age ranged from 20 to 60 years (mean 33.5 years) participated in study. Out of these 31 were male (68.89%) and 14 were female (31.11%). 44.44% (20) of cases had mild head injury (mean aged 32.30years) and rest of patients 55.55%(25) had moderate head injury (mean aged 34.44years). Among 20 patients with mild injury, 14 (70%) were male and 6 (30%) were female. Out of 25 patients with moderate head injury, 17 were male (68%) and 8 were female (32%). The mean age and the gender distribution within the two groups (mild and moderate TBI) had no statistically significant difference.

Majority of patients (72%) sustained head injury because of road traffic accident followed by assault (25%) and 6 patients (3%) had fall from height. ^{1}H MR spectroscopy of bilateral basal ganglia was performed during sub acute period. Average time to perform MRS was 8.8 days (range 7-15 days). Out of total 45 patients, 24 patients (53.33%) showed good recovery (Glasgow outcome scale 5), 12 patients (26.67%) had moderate disability (GOS- 4), 8 patients (17.78%) had severe disability (GOS- 3), one patient (2.22%) had persistent vegetative state (GOS- 2).

Good and less than good recovered patients: Mean age was 32.13 years in patients who showed good recovery and 35.05 years in patients who had less than good recovery (p =0.38). Among patients(24) who showed good recovery, 18 (75%) were male. In less than good recovered patients (21), 13(61.90%) were male and 8 were female.

TABLE1: Metabolite ratios in mild and moderate head injury.

S.NO.	Metabolites ratio	Mild TBI n=20 (GCS 13-15)	Moderate TBI n=25 (GCS 9-12)	P value
1.	Mean NAA/Cr	1.66	1.63	0.61
2.	Mean Cho/Cr	1.23	1.33	0.18
3.	Mean NAA/Cho	1.42	1.23	0.24

TABLE 2: Glasgow Outcome Score & Ratios of NAA/Cr, Cho/Cr, NAA/Cho

S. No.	Glasgow Outcome Score	Mean NAA/Cr	Mean Cho/Cr	Mean NAA/Cho
1.	5 (n=24)	1.77	1.10	1.64
2.	4(n=12)	1.54	1.42	1.09
3.	3(n=8)	1.43	1.58	0.91
4.	2(n=1)	1.42	1.6	0.89

TABLE3: NAA/Cr, Cho/Cr, NAA/Cho Metabolite ratios in good and less than good recovered patients.

S. No.	Recovery (GOS 1-5)	NAA/Cr	Cho/Cr	NAA/Cho
1.	Good (5) n=24	1.77	1.10	1.64
2.	Less than good (1-4) n=21	1.49	1.49	1.01
3	P value	<0.0001	<0.0001	<0.0001

Statistically significant correlation exists between metabolite ratios of NAA/Cr, Cho/Cr & NAA/Cho with outcome (Glasgow outcome score).

DISCUSSION: Traumatic brain injury is a common cause of neurological morbidity and mortality. However, conventional imagings (CT/MRI) have limited importance in predicting outcome. This can be explained by the microscopic tissue damage at cellular level which is not detected by conventional imaging. ^{1}H MRS provides in vivo measures of brain metabolites. So this study was conducted and metabolite ratios were correlated with GCS and GOS. NCCT head was done on presentation and in sub acute period 1H MR Spectroscopy was done. Metabolite ratios of NAA/Cr, Cho/Cr, NAA/Cho were obtained in bilateral basal ganglia. A total of 45 cases were included and followed up. Outcome was assessed by Glasgow Outcome Scale at least after 3 months of injury.

Mean age of patients in our study was 33.5 years and 68.89% were male. In most of the studies, mean age was in 3rd or 4th decade most of the victims are male.[1,10,11,16-19] Mean age was 53 years in the study conducted by Friedman and Brooks[14] and mean age 25.6 years by Mar Ariza's study[20]. In our study, majority of head injury was due to road traffic accidents (72%). In a study conducted in Bangalore, the authors also concluded that road traffic injuries (RTIs) (59%), falls (25%) and violence (10%) were the major causes of neurotrauma.[21] We included only patients with mild and moderate traumatic brain injury but Govindraju et al[18] and Kubas [19] included patients with mild TBI (GCS >13). In other studies, subjects with more severe head injuries were included. [11,13,20]

In our study, patients were subjected for MR spectroscopy in subacute period once they became clinically stable and mean period was 8.8 days (range 7-15 days). ^{1}H MR spectroscopy study had been done in acute, subacute periods and late after trauma by different researcher like Ross BD et.al [22] in acute period, Friedman, Brooks et al[13] in sub acute to chronic (mean 52.7 days), Govindaraju et al [18] in 2-30 days (mean 13.3 days), Silvia Marino et al [23] in48-72 hrs, Yanli Du et al [24] in Early (mean 9.5 d) phase.

In our study, ^{1}H MRS was done at the level of basal ganglia. Single voxel of size 2×2×2 cm^3 was placed on right and left basal ganglia and metabolite ratios of NAA/Cr, Cho/Cr and NAA/Cho was measured. Basal ganglia is very sensitive to hypoxic, ischemic, molecular and metabolic events associated with traumatic brain injuries. In a study conducted by Mar Ariza et.al, 2 voxels were placed, one in left basal ganglia and other in the left mid temporal region.[23] In other studies, voxels have been placed in different regions of brain. Ross Bd et al[22] in Parietal white matter and Occipital grey matter, Friedman, Brooks et al [13] in Occipito parietal white & occipital grey matter, Govindaraju et al[18] volumetric proton MRS, Silvia Marino et al [23] Multi voxel, Yanli Du et al [24] posterior part of frontal lobe white matter etc.

So we could not find any statistically significant difference in metabolite ratios Mean NAA/Cr, Cho/Cr and NAA/Cho and GCS (clinical status). This is in keeping with the study done by Grant Sinson et al.[17]. In that study, NAA/Cr ratio was obtained from splenium of corpus callosum. No significant correlation was found between NAA/Cr ratio and GCS. However, they had not studied other metabolite ratios. [17]

In the study conducted by Govindaraju et al [18] similar results were found. In their study, distributions of N-acetylaspartate (NAA), total creatine (Cr), and total choline (Cho) were mapped over a wide region of the brain, and metabolite ratios were calculated for 25 regions without MR imaging abnormalities. Results were compared with data from 13 control subjects. Significant changes ($P < 0.05$) were found for some, but not all, brain regions for the average values from all MTBI subjects, with reduced NAA/Cr, increased Cho/Cr, and reduced NAA/Cho. Global NAA/Cho obtained from the sum of all sampled regions in two subjects was significantly reduced. They conclude that metabolite ratios were not significantly correlated with GCS score at admission. In the whole brain proton MRS imaging of mild to moderate TBI study conducted by Varan Govind et.al, no significant correlation were found between any of the MRSI or NPT measures and the GCS [25]

In contrast to our study, Silvia Marino et.al [23] found significant correlation between metabolite ratios and GCS. Proton magnetic resonance spectroscopic imaging (^{1}H MRSI) examinations were performed in 10 patients with TBI 48–72 h after the trauma, to obtain early measurements of central brain levels of N-acetylaspartate (NAA), choline (Cho), creatine (Cr) and lactate (La). NAA ratios were found to be significantly lower in patients with TBI than in normal controls. In contrast, Cho ratios were significantly higher in patients with TBI than in normal controls. Increased La levels were found in 5 of 10 patients with TBI. Both NAA and La values correlated closely with those of the Glasgow Coma Scale at presentation ($r = 0.73$ and -0.62, respectively; $p<0.01$ for both) and the Glasgow Outcome Scale at 3 months ($r = -0.79$ anand 0.79, respectively; $p<0.01$ for both). Similar contradictory results were also found by Yanli Du et al[24] In that study, proton spectra were acquired from the posterior part of normal-appearing frontal lobes having predominantly white matter in 72 patients with severe TBI within a few days of trauma, mean 9.5 days and also in 30 controls.

^{1}H-MRS studies revealed lower ratios of N-acetylaspartate (NAA)/Choline (Cho) and NAA/ Creatine (Cr) and higher ratios of

Cho/Cr in patients with TBI when compared to the control group. In patients with severe TBI, NAA/Cr, NAA/Cho and Cho/Cr ratios were significantly correlated with the initial GCS score. (P=0.004, r =0.439, P=0.018, r =0.364, P=0.004, r = -0.762, respectively). These contradictory results may be due to difference in time frame and inclusion of subjects with more severe injury.

^{1}H MR Spectroscopy Metabolite Ratios and Outcome Assessment: We have assessed outcome based on Glasgow outcome scale at least 3 months after injury and Metabolite ratios of NAA/Cr, NAA/Cho and Cho/Cr were correlated to outcome. We found a statistically significant correlation with ratios of NAA/Cr, NAA/Cho and Cho/Cr and outcome of patients. This is in keeping with the study done by Mar Ariza et.al[20] In their study, metabolite concentrations were acquired from voxels localized at 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 neuropsychologi cal assessment. They found that NAA/Cho 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. In our study, NAA/Cr and Cho/Cr ratios were also measured and outcome assessment was done by GOS of 5 which reflects good neuropsychological functioning.

Correlation of outcome with proton MR spectroscopic finding from other regions of brain also has similar results**.** Friedman, Brooks et al [13] measured N-acetylaspartate (NAA), creatine, and choline in normal-appearing occipitoparietal white and occipital gray matter using short-echo quantitative spectroscopy. Patients with TBI displayed reduced NAA in white matter and elevated choline in gray matter, suggestive of neuronal injury and inflammation, respectively. NAA and creatine in white and gray matter were significantly associated with composite neuropsychological function and many individual neuropsychological tests. Gray matter choline, although abnormal, was not related to neuropsychological function.

Garnett et al [11] also found that NAA/Cr acquired at the early time point significantly correlated with the clinical outcome of the patients, assessed using either the Glasgow outcome scale (P = 0.005, n = 17) or the disability rating scale (P < 0.001, n = 17). They concluded that there is a sustained alteration in NAA and Cho. These findings provide possible evidence for cellular injury (NAA loss reflecting neuroaxonal cell damage and raised Cho and Ins reflecting glial proliferation) not visible by conventional imaging techniques[11]. Similar results were also obtained by Grant Sinson et al. [17] Thirty patients with TBI were studied on a 1.5-T system with magnetization transfer imaging and MR spectroscopy of the splenium. The splenium of the corpus callosum and brain stem were studied because these are often affected by diffuse axonal injury. Scans were obtained 2 to 1129 days after injury (median, 41 days). MTR was considered abnormal if it was more than 2 SD below normal. Proton MR spectroscopy was used to calculate the *N*-acetylaspartate (NAA)/creatine (Cr) ratio. GOS was determined at least 3 months after injury. In 10 patients with a GOS of 1 to 4, the mean NAA/Cr was 1.24 ± 0.28; two of these patients had abnormal MTR in normal-appearing white matter (NAWM). In 20 patients with a GOS of 5, the mean NAA/Cr was 1.53 ± 0.37 ($P < .05$); four of these patients had abnormal MTR in NAWM. MTR abnormalities in NAWM were identified in six patients, but these changes did not correlate with GOS or MR spectroscopy changes. They concluded that MTR and MR spectroscopy can quantify damage after TBI, and NAA levels may be a sensitive indicator of the neuronal damage that results in a worse clinical outcome[17].

M Uzan et al[15] suggested that the NAA/Cr ratio within the thalamus was significantly lower in patients who remained in persistent vegetative state. In contrast to our study, they could not found any correlation with Cho/Cr ratio. It could be because of the fact that examination was done after 6-8 months of injury. Govindaraju et al also found a weak correlation between ratios of NAA/Cr, NAA/Cho and Cho/Cr and GOS score at discharge[18]. Varan Govind et al also demonstrated that significant and widespread alterations of brain metabolites occur as a result of mild-to-moderate TBI, and that these measures correlate with measures of cognitive performance.[25] In study conducted by Yanli Du et al [24] proton spectra were acquired from the posterior part of normal-appearing frontal lobes having predominantly white matter in 72 patients with severe TBI within a few days of trauma, mean 9.5 days and also in 30 controls. 1H-MRS studies revealed lower ratios of N-acetylaspartate (NAA)/Choline (Cho) and NAA/ Creatine (Cr) and higher ratios of Cho/Cr in patients with TBI when compared to the control group. In patients with severe TBI, NAA/Cr, NAA/Cho and Cho/Cr ratios were significantly correlated with the clinical outcome, Glasgow Outcome Scores (GOS) (P=0.006, r =0.414; P=0.007, r =0.412; P=0.016, r = -0.775, respectively). They concluded that ^{1}H-MRS may be a novel method of assessing brain function, estimating coma duration, and predicting outcome in patients with severe TBI.

CONCLUSION: Our study population comprised of patients with age ranged from 20-60 years, most common involved were male (68.89%). Patients with mild and moderate head injury & good and less than good outcome were similar in respect to age and sex. Majority of patients (72%) sustained head injury because of road traffic accidents. ^{1}H MR spectroscopy of bilateral basal ganglia was performed during sub acute period with a mean of 8.8 days (range 7-15 days). Metabolite ratios of NAA/Cr, Cho/Cr & NAA/Cho did not show any correlation with Glasgow coma scale(clinical status). However, Statistically significant correlation exists between metabolite ratios of NAA/Cr, Cho/Cr & NAA/Cho outcome (Glasgow outcome score).

LIMITATIONS OF THE STUDY: Patients with severe TBI were not included in our study. Further studies with larger sample size is required to make more conclusive results.

FINANCIAL SUPPORT AND SPONSORSHIP: Nil
CONFLICTS OF INTEREST: There are no conflicts of interest.

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