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Evaluation of the association between brain metabolites and cognitive condition in patients with mild traumatic brain injury using magnetic resonance spectroscopy

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Abstract

Background: The relationship between neurometabolic changes after mild traumatic brain injury (mTBI) and psychological disorders is not well defined.

Objectives: The aim of this study was to compare the relationship between the neurometabolic state of the brain and cognitive tests in mTBI patients and healthy individuals.

Methods: This cohort study included 21 mTBI patients (exposed group) and 21 individuals without trauma (non-exposed group).The demographic and trauma information of patients including age, sex, the mechanism of trauma and the GCS score were recorded. Then, the psychological status of the two groups were evaluated by Wechsler, Stroop, and Wisconsin test. Moreover, the levels of neurometabolites were measured by magnetic resonance spectroscopy (MRS). Data were analyzed by SPSS software and $P<0.05$ was considered statistically significant.

Results: The amount of brain metabolites (NAA, choline, creatine, Chol/Cr ratio and NAA/Cr ratio) in the white matter of bilateral frontal lobe in the two exposer and non-exposer groups had no significant difference ($P>0.05$). Additionally, there was a significant difference between the two groups regarding the correct answers of the Wisconsin test ($p=0.027$), and the time to complete the Stroop test ($p=0.009$). No significant difference was observed in the Wechsler memory test score between the two groups ($p>0.05$).

Conclusion: Mild TBI does not lead to changes in brain metabolites in the acute phase after trauma. However, the scores of psychological tests of Stroop and Wisconsin in mTBI patients had a statistically significant difference with healthy individual.

Keywords: Traumatic Brain injury, Magnetic Resonance Spectroscopy, Brain metabolites, Psychological status.

Introduction

Traumatic Brain injury (TBI) is one of the main causes of death and disability, which accounts for about 30% of all deaths caused by trauma. It is estimated that around 4.48 million people die from trauma each year, with about 2 million deaths attributed to TBI. In the United States, more than 2.8 million cases of TBI occur annually, with a mortality rate of 2%.[1] In a review study in 2023, the incidence rate of TBI in Iran was reported to be 15.3 to 144 per 100,000 population and the mortality rate due to TBI was estimated to be 10.4%. Based on the Glasgow Coma Scale (GCS), TBI is classified into three categories: mild, moderate, and severe.[2] It seems that 75-80% of injuries related to TBI are mild and characterized by a score of 13

to 15 on the Glasgow Coma Scale.[3] Most of mild traumatic brain injury (mTBI) cases are considered as injuries without bleeding or with little bleeding, and a significant percentage of them are undetectable by computed tomography scan (CT Scan) or magnetic resonance imaging (MRI).[4,5]

Inability to accurate diagnosis of mTBI in the acute phase results in an increase in the number of patients with symptoms of post-traumatic stress disorder (PTSD), depression and other neurological and cognitive disorders in the first months after trauma.[6] The long-term effect of mTBI on patients and their families is a multifaceted problem that threatens their physical, social and psychological health and ultimately causes economic burden.[7]

Most mTBIs are caused by angular or rotational acceleration or brain tissue tearing as a result of loss of connection between the axons of neurons.[8,9] Therefore, their effects are not necessarily localized and many of them may cause widespread diffuse effects on the entire brain parenchyma. Various studies have shown that a large number of complications of mTBI are caused by secondary damage and consequences such as diffuse axonal injury (DAI),[10,11] inflammation,[12] edema,[13] apoptosis,[14] aggravation of toxicity,[15] mitochondrial defects[16,17] and neurometabolic changes.[18]

Physiological and biochemical changes that occur at the cellular level are rarely detected by CT or MRI techniques.[5] Therefore, a detailed evaluation of mTBI is needed for a deeper understanding of changes at the molecular level. These molecular changes can lead to changes in biochemical processes that cause macroscopic changes at the tissue level.

Magnetic resonance spectroscopy (MRS) is one of the non-invasive methods that have the potential to evaluate metabolic changes at the cellular level in patients with mTBI.[19]

Several studies identified neurometabolite changes caused by mTBI, and the most important finding was significant decrease in the amount of the N-acetyl Aspartate (NAA) in the gray and white matter of the brain.[20-25]

Studies related to cell membrane markers such as choline (Cho) are controversial. So that some studies have shown an increase in choline in different regions in the brain parenchyma,[20,26] while other studies did not observe a change in choline levels in mTBI.[22,23,27]

It is believed that amount of total cellular creatine is constant in most brain damages, therefore normalizing the ratio of MRS metabolites to total creatine is a common practice.[28] Despite this, two studies have reported increased white matter creatine in patients with mTBI.[27,29]

Although, some of patients with mTBI have good performance, a significant part of these patients have experienced cognitive changes in the first hours following the trauma[30] and depression a few months after the injury.[31] It has been reported that at 3–5 days after injury, patients with mTBI performed significantly worse compared to orthopedic injury or healthy controls in different cognitive tasks, such as immediate recall, short-delayed recall, long-delayed recall, attention, working memory, processing speed and other executive functions.[32,33] However, some deficits may be detected even 1 year after the trauma.[34,35] Therefore, these patients need special attention.

In several studies, the association between neurometabolites and psychological status in TBI patients were assessed.[26-28,33,36] The results of a study conducted by George et al. in patients with mTBI during acute phase showed that metabolic measurements in the thalamus and centrum semi oval areas could be used as diagnostic and prognostic markers for mTBI. In this research, ANAM was used for psychological evaluation of patients. The ANAM is a neurocognitive test to evaluate a number of cognitive domains including attention, concentration, reaction time, memory, processing speed, decision-making, and executive function. In this study only Cr level had positive correlation with two ANAM subsets.[28] Another study in moderate to severe TBI patients at 1.5 months after injury showed a positive association between the Cr level in gray matter and their neurocognitive performance.[36] Moreover, the results of Sivac et.al study conducted on mTBI patients showed that NAA and NAA/Cr levels in frontal lobe were decreased during 24-72 h after injury. The results of Wechsler and Stroop tests were significantly different between mTBI patients and healthy individual and these two tests had a significant correlation with NAA and NAA/Cr levels.[33] In contrast, the studies by Yeo et al.,[29] and Henry et al.,[25] did not find any correlation between neuropsychological tests and brain metabolites.

Objectives

Today, we know that mTBI can affect the social, emotional, and cognitive status of trauma patients but evidence on the relationship of neurometabolic changes after mTBI and psychological status is not well known and more studies need to be performed to examine the effects of these changes on overall function of the brain. Therefore, the present study was conducted to investigate

the relationship between brain neurometabolic status and psychological state in the mTBI patients.

Methods

This cohort study involved two groups: one exposed and one non-exposed. The exposed group consisted of 21 patients with mTBI who were transferred to Shahid Beheshti Hospital in Kashan, Iran. The criteria for entering the study included an age range of 15-65 years, GCS range of 13-15, an education level of secondary school, consciousness less than 30 minutes after trauma, amnesia less than 24 hours after trauma, a normal CT scan of the brain or CT with brain hemorrhagic findings, no previous history of brain trauma, no history of taking psychotropic drugs and the absence of brain tumor or congenital brain disorders. The exclusion criteria encompass individuals who did not take part in the follow-up periods of the study or those who had a phobia of the MRI machine.

First, the demographic and trauma information of the patients, including age, sex, mechanisms of trauma, and GCS score, were recorded. Then, the patients were asked to return within a week after discharge to evaluate psychological disorders using Wechsler, Stroop, and Wisconsin numerical memory subtests, and to perform MRS. The control group consisted of 20 individuals without trauma who visited the hospital for MRIs of body organs other than the brain. They also underwent MRS and psychological assessments within a week of their hospital visit.

Magnetic resonance spectroscopy was performed by a Philips 1.5 Tesla machine. The MRS protocol includes sequences of T1-Weighted Volume axial series (TE = 6.9 msec, TR = 17.7 msec, 1.5 mm slices), T2 Weighted Axial series (TE = 30/100, TR = 2800 msec), 3D phase encoded point resolved spectroscopy (3D PRESS) (TE = 135, TR = 1300). Then, MRS was prepared from the voxels in the white matter of bilateral frontal lobes. LC Model software was used offline to check the MRS spectra. LC Model is software that processes MRS frequencies and compares the amount of spectra measured in vivo to the linear combination of different spectra with the in vitro basis. The software uses a model that includes linear shapes and basic functions.[37] Metabolites evaluated included NAA, a marker for neuronal integrity; choline (chol), a marker for increased cell membrane turnover; and creatine (cre), a marker for enhanced cognitive function.

The psychological tests used in this study included Wechsler, Stroop, and Wisconsin numerical memory subtests. These tests evaluate the cognitive functions, which are more affected patients after mTBI.[33]

The Wechsler IQ test is one of the intelligence tests that can determine both the overall intelligence score of a person and the level of a person's ability in two scales of verbal skills and practical skills. The verbal scale of the Wechsler IQ test uses seven parts. A different scale identifies a person's intelligence score in the field of verbal skills. Each subscale consists of several questions and will have a specific score. According to the number of questions that the subject answered correctly in each subscale and according to the importance of the person's answer, his raw score in each subscale is determined. Based on the Wechsler intelligence test table, the raw scores are converted into aligned scores, and then the verbal intelligence score of the person is determined from the sum of these aligned scores. The non-verbal scale of the Wechsler IQ test also has six subtests and measures skills, such as spatial perception and speed of action.[38]

The reliability of split half of the WAIS-R was 0.97 for total intelligence, 0.97 for verbal intelligence, and 0.93 for performance intelligence. The test-retest reliability coefficients with an interval of 1-7 weeks were reported as 0.97 for total intelligence, 0.97 for verbal intelligence, and 0.93 for performance intelligence.[39] In Iran, the test-retest reliability coefficient for the subtest was reported to be between 0.58 and 0.87, while the reliability coefficient for intelligence coefficients ranged from 0.76 to 0.94.[40]

The Stroop test is a widely used and famous method in analysis and research that reveals the different functions of the brain and its absolute and cognitive work. This test was used to assess the cognitive processing speed. First, the participant reads a list of colors, but the color of the word is different from the meaning of the word itself. For example, the word "orange" is correct in terms of writing, but it is written in green color. The participant records the duration of reading the words. Next, the participants must repeat the test with the new list of words but must read the printed colors of each word. Therefore, when the word "orange" is printed in green, the participant must read "green" and continue reading the words. Using this model, we can assess a person's cognitive processing speed, their attention capacity, and their level of cognitive control (otherwise known as their executive function).[38] The validity and reliability of the Stroop test have been demonstrated in several studies.[41,42]

Wisconsin test: The Wisconsin test is a neuropsychological instrument used to measure the executive functions, reportedly sensitive to brain dysfunction affecting the frontal lobes. This test consists of 64 cards on which one to four symbols in the form of a red triangle, a green star, a yellow cross and a blue circle are

engraved, and none of the two cards were similar or repeated. The subject's duty is to place the cards based on the inference from the pattern used by the examiner. The test results produce a number of useful psychometric scores, including numbers, percentages, and percentiles of: categories achieved, trials, errors, and perseverative errors.[38]

Data analysis

All statistical analyses were performed with SPSS (version 16.0, SPSS Inc, Chicago, IL, USA). First, the distribution of data in each study group was examined. Among the examined cases, the choline metabolite of the right and left frontal lobe had an abnormal distribution, so the logarithm of the values was used to normalize the distribution. Considering that in this study two "Peak" waves of creatine were measured; the total values were used. Chi-square test or t-test and its non-parametric equivalent were used to compare the two groups. Moreover, linear regression model was used to control the effect of confounding variables. A “P-value” less than 0.05 was considered significant.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. This study has been approved by the ethics committee of Kashan University of Medical Sciences (ethical code: IR.KAUMS.MEDNT.REC.1400.186). The patients' information was completely confidential and since there was no intervention other than common imaging procedures, there were no ethical restrictions. In order to perform psychological tests, the consent was obtained from the studied subjects.

Results

The mean age of the study subjects in the non-exposure and exposure groups was 39.35 and 28.9 years, respectively, with a significant difference observed between the two groups (P=0.012). 85% of the individual in the exposure group and 55% of the individual in the non-exposure group were men, and there was a significant difference between the two studied groups (P=0.038). In terms of education, 95% of the individual in the exposure group were under diploma, while the majority of individual in the non-exposure group (70%) had university education and there was a significant difference between the two studied groups (P<0.001).

Brain metabolites

Table 1 shows that there was no significant difference between the mean and standard deviation of neurometabolites (NAA, choline, creatine, Chol/Cr ratio and NAA/Cr ratio) in the white matter of the bilateral frontal lobes in the exposure and non-exposure groups (P>0.05).

Table 1. Comparison of brain metabolites in the white matter of the right and left frontal lobes in two groups

Metabolite	Frontal Lobe	Groups		Mean Difference	P value*
		Exposed Mean± SD	Non-Exposed Mean± SD		
NAA (dmol)	Right	0.061±0.013	0.061±0.010	0.0017	0.643
	Left	0.061±0.010	0.056±0.013	0.0046	0.282
Choline	Right	0.037±0.009	0.034±0.008	0.031	0.359
	Left	0.035±0.008	0.033±0.009	0.398	0.280
Creatine	Right	0.044±0.016	0.041±0.008	0.0031	0.470
	Left	0.043±0.014	0.040±0.008	0.0025	0.528
NAA/ Cr	Right	1.481±0.283	1.479±0.158	0.0019	0.979
	Left	1.520±0.360	1.402±0.174	0.118	0.205
Chol / Cr	Right	0.887±0.194	836±0.106.0	0.051	0.314
	Left	0.878±0.195	0.818±0.151	0. 0601	0.292

NAA: N-acetyl Aspartate, Cho: choline, Cr: Creatine. Significant level: P<0.05

Psychological status

As shown in Table 2, there was a statistically significant difference between the two groups concerning the mean values and standard deviations of the Wechsler memory test score, the Wisconsin test score (number of correct answers), and the Stroop test score (test duration) (P<0.05). This result indicated that trauma had an effect on memory and cognition.

Table 2. Comparison of psychological status in two groups

Groups	**Exposed,** Mean± SD	**Non-Exposed,** Mean± SD	**P value**
Tests			
Wechsler memory test score	9.85±2.05	12.6±3.67	0.007
Wisconsin test score (correct answers)	29.75 ±5.63	32.9 ±3.68	0.044
Wisconsin test score (wrong answers)	23.25± 6.93	19.35 ±7.10	0.087
Wisconsin test score (test time)	177.13± 58.39	147.93 ±80.36	0.197
Stroop test score (time)	109.78± 28.48	134.45 ±24.13	0.006

The findings indicated that there was no statistically significant difference between the exposure and non-exposure groups concerning the mean and standard deviation of the Wisconsin test score (the number of incorrect answers and the duration of the test) (P>0.05). Furthermore, a linear regression analysis was used to control the confounding variables of age, gender and education. Findings showed that after controlling confounders, there was no correlation between the amount of NAA, choline, creatine, NAA/Creatine and chol/cre in the white matter of right and left frontal lobes with head trauma (P> 0.05) [Tables 3, 4, 5, 6 and 7].

Considering that in this study, the amount of metabolites was not a mediator variable; the relationship between mTBI and psychological tests was investigated.

Table 3. Correlation between trauma and NAA level in right and left frontal white matter

NAA levels in the right frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	- 0.0001	0.0001	-0.79	0.436	- 0.0001 - 0.0002
Female Sex	- 0.0002	0.004	0.05	0.957	- 0.009 - 0.009
University Education	- 0.006	0.005	-1.11	0.274	- 0.0179 - 0.005
Exposure group	- 0.004	0.006	-0.68	0.502	- 0.016 - 0.008
Constant	0.070	0.009	7.21	0.000	0.050 - 0.090
NAA levels in the left frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	- 0.0001	0.0002	-0.60	0.553	- 0.0005 - 0.0003
Female Sex	- 0.002	0.005	-0.53	0.602	- 0.013 - 0.007
University Education	0.001	0.006	0.24	0.810	- 0.011 - 0.014
exposure group	0.003	0.007	0.44	0.660	- 0.011 - 0.017
Constant	0.062	0.011	5.64	0.000	0.039 - 0.084

Table 4. Correlation of trauma with the amount of choline in the right and left frontal white matter

Choline levels in the right frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	0.002	0.001	1.68	0.12	- 0.0005 - 0.005
Female Sex	- 0.004	0.038	-0.12	0.98	- 0.082 - 0.073
University Education	0.037-	0.047	-0.079	0.437	- 0.134 - 0.059
Exposure group	0.040	0.052	0.78	0.443	- 0.066 - 0.147
Constant	1.555-	0.082	18.93	0.000	-1.722 - - 1.388
Choline levels in the left frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	0.0012	0.0018	0.70	0.490	- 0.002 - 0.004
Female Sex	- 0.030	0.043	-0.69	0.495	- 0.018 - 0.058
University Education	0.023-	0.054	-0.044	0.664	- 0.133 - 0.086
Exposure group	0.031	0.059	0.053	0.600	- 0.089 - 0.152
Constant	-1.516	0.092	16.33	0.000	-1.705 – 1.327

Table 5. Correlation of trauma with creatine level of right and left frontal white matter

Creatine levels in the right frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	0.0001	0.0002	0.76	0.452	- 0.0002 - 0.0005
Female Sex	- 0.001	0.005	-0.36	0.721	- 0.012 - 0.008
University Education	0.0016-	0.006	-0.026	0.800	- 0.014 - 0.011
Exposure group	0.0035	0.0069	0.51	0.612	- 0.010 - 0.011
Constant	0.036	0.010	3.35	0.002	0.014 - 0.058
Creatine levels in the left frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	0.0001	0.0001	0.56	0.580	- 0.0002 - 0.0005
Female Sex	- 0.005	0.004	1.10	0.279	- 0.0044 - 0.014
University Education	0.001-	0.005	-0. 25	0.803	0.013 - 0.010
Exposure group	0.004	0.006	0.73	0.471	0.008 - 0.017
Constant	0.034	0.010	3.43	0.002	0.014 - 0.055

Table 6. Correlation of trauma with NAA / Creatine ratio in right and left frontal white matter

NAA / Creatine ratio levels in the right frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	-0.008	0.0034	-2.57	0.015	- 0.015 - -0.0018
Female Sex	- 0.040	0.082	0.49	0.629	- 0.127 - 0.208
University Education	0.119-	0.102	-1.17	0.251	- 0.127 - 0.208
Exposure group	0.175-	0.112	-1.56	0.129	- 0.403 - 0.053
Constant	1.89	0.176	10.77	0.000	1.53 - 2.25
NAA / Creatine ratio levels in the left frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	-0.007	0.004	-1.68	0.103	- 0.016 -0.0015
Female Sex	- 0.068	0.105	-0.65	0.519	- 0.284 - 0.146
University Education	0.040-	0.131	0.31	0.759	- 0.225 - 0.307
Exposure group	0.025-	0.144	0.18	0.859	- 0.267 - 0.318
Constant	1.702	0.225	7.55	0.000	1.244 - 2.160

Table 7. Correlation of trauma with Choline / Creatine ratio in right and left frontal white matter

Choline / Creatine ratio levels in the right frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	0.002	0.002	0.92	0.362	0.002 -0.007
Female Sex	0.013	0.060	0.22	0.826	- 0.109 - 0.136
University Education	0.032-	0.074	0.44	0.666	- 0.185 - 0.119
Exposure group	0.065	0.082	0.79	0.434	- 0.102 - 0.232
Constant	0.759	0.128	5.89	0.000	0.497 - 1.021
Choline / Creatine levels in the left frontal white matter					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	-0.0002	0.002	-0.10	0.920	-0.006 -0.005
Female Sex	-0.056	0.067	-0.84	0.407	- 0.194 - 0.080
University Education	0.041-	0.083	-0.050	0.624	- 0.212 - 0.129
Exposure group	0.011	0.092	0.13	0.900	- 0.175 - 0.199
Constant	0.885	0.144	6.13	0.000	0.591 - 1.178

The findings indicated that after controlling for confounders, there was no correlation between the Wechsler memory test score and the score of incorrect answers and the duration of the Wisconsin test with brain trauma (P>0.05). However, the score of the Wisconsin test for correct answers (p=0.027) and the duration of the Stroop test (p=0.009) showed a significant difference between the two groups [Table 8].

Table 8. Correlation between trauma and psychological tests

Wechsler test score (correct answers)					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	-0.016	0.044	-0.37	0.717	-0.107 -0.074
Female Sex	2.219	1.059	2.10	0.043	0.069 - 4.370
University Education	1.329	1.321	1.01	0.321	- 1.353 – 4.011
Exposure group	-1.423	1.457	0.98-	0.335	- 4.383 – 1.535
Constant	11.314	3.277	4.97	0.000	6.690 - 15.938
Wisconsin test score (correct answers)					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	-0.172	0.068	-2.52	0.016	-0.312 - -0.033
Female Sex	1.792-	1.621	-1.11	0.277	-5.084 – 1.499
University Education	1.049	2.022	0.52	0.607	- 3.056 – 5.156
Exposure group	-5.159	2.232	2.31-	0.027	- 9.690 – 0.627
Constant	39.778	3.487	11.41	0.000	32.699 - 46.858
Stroop test score (time)					
Independent Variables	**Correlation Coefficient**	**Standard Error**	**t statistic**	**P-value**	**95% confidence Interval**
Age	0.893	0.401	2.22	0.033	0.076 -1.709
Female Sex	-4.495	9.623	-0.47	0.643	-24.051 -15.061
University Education	2.647	11.922	0.22	0.826	- 21.581 -26.786
Exposure group	36.399	13.104	2.78	0.009	9.767 -63.631
Constant	74.562	20.499	3.64	0.001	32.901 -116.222

Discussion

Findings indicated no significant difference in the levels of neurometabolites NAA, choline, creatine, the choline/creatine ratio, and the NAA/creatine ratio in the white matter of the bilateral frontal lobes between patients with mTBI and healthy individuals. Several studies have examined the levels of NAA, choline, and creatine, as well as the NAA/Cr and Cho/Cr ratios in various regions of the brain following TBI.[20-28, 33, 36] In the study by Brooks et al., cognitive and metabolic responses to moderate and severe TBI were assessed. The levels of N-acetyl aspartate, choline, creatine, and myo-inositol were measured in the gray matter of the occipito-parietal region and the white matter of the parietal lobes. The results indicated a decrease in NAA levels in patients compared to the control group after 1.5 months. However, at 3 and 6 months post-injury, NAA levels increased, suggesting metabolic recovery.[36] Consistent with our findings, another study reported no difference in NAA levels between mTBI patients and the control group.[21]

A study by Sivak et al.,[33] compared mTBI patients at 24-72 hours post-injury with healthy individuals and concluded that the NAA level and NAA/Cr ratio in the frontal lobes of mTBI patients were lower than in the control group. However, other metabolites, such as the Cr level and Cho/Cr ratio, showed no change, which aligns with our study results. In a study by Vaganozi et al.,[22] that measured neurometabolites in the frontal lobes of the brain three days after TBI, a decreased level of NAA/Cr was observed. Conversely, another study[43] reported increased levels of Chol/Cr and NAA/Cr. Results from Henry et al. studies also indicated that during the six days following mTBI, the NAA/Cr level in the prefrontal cortex decreased.[24,25] In the study conducted by Gasparovic et al., the splenium and supraventricular regions were selected for measuring neurometabolites during days 3-19 post-TBI, revealing an increase in creatine levels without any change in NAA and choline levels.[27] Additionally, in the Govind et al. study, choline levels showed an increase in patients with moderate TBI.[26] However, several studies[22,23] did not observe any change in the choline levels in mTBI, which is consistent with our findings.

In a study conducted by George et al.,[28] during the early and late sub-acute phases (10 to 30 days) and also 6 months

after mTBI, it was revealed that the Cr levels and the NAA/Cr ratio in the thalamus and centrum semiovale showed no significant difference compared to healthy individuals. A decrease in the Cho/Cr ratio was observed in the late sub-acute phase. This finding aligns with our results regarding the Cr levels and NAA/Cr .

The reasons for the discrepancies between our results and those of other studies may stem from differences in the timing and brain regions assessed for neurometabolites. For instance, we measured neurometabolites in the white matter of the frontal lobes during the first week after TBI, whereas in the study by Brooks et al.,[36] neurometabolites were measured at 1.5, 3, and 6 months post moderate TBI in the gray matter of the occipito-parietal region and the white matter of the parietal lobes. Additionally, variations in the severity of TBI could be another contributing factor. Considering that the present study focused on patients with mTBI, it is possible that the force from the trauma primarily impacted the more superficial layers of brain tissue (gray matter), while the deeper regions were less affected. Furthermore, differences in MRS techniques, such as single versus multiple voxel methods and post-processing techniques, sample sizes, and study populations may also account for these contrasting findings.

According to the results of the present study, the absence of a significant difference in brain metabolites between the exposure and non-exposure groups made it impossible to explore the relationship between brain metabolites and cognitive changes. Consequently, we investigated the relationship between brain trauma and psychological changes.

Results from the psychological tests (Wisconsin, Stroop, and Wechsler memory subtests) conducted in the first week following the TBI, when compared to healthy individuals, indicated a statistically significant difference between the two groups in terms of the number of correct answers on the Wisconsin test and the duration of the Stroop test. Specifically, the number of correct answers in the mTBI group was significantly lower than that of healthy individuals, while the duration of the Stroop test in the mTBI group was longer than that in the healthy group. In other words, there was a significant decrease in the executive functions of the brain (which encompass a set of abilities that control, monitor, and coordinate more basic cognitive processes, playing a crucial role in complex reasoning, learning, and decision-making), and a reduction in the speed of cognitive processing during the acute phase after mTBI compared to healthy individuals.

Consistent with the findings of the present study, Sivak et al., concluded that the results of Stroop tests were significantly different between mTBI patients and healthy individuals.[33] Furthermore, another study found that patients with mTBI performed worse across all scales of the Stroop test compared to healthy individuals. Therefore, mild traumatic brain injury can disrupt the executive functions of the brain's prefrontal lobes.[44] However, a study by Ord et al. showed that one year after the trauma, there was no significant difference between mTBI patients and the control group in Wisconsin Card Sorting Test (WCST) performance, although increased levels of impairment were observed in the moderate-to-severe TBI group.[45] This discrepancy in results may be attributed to the differences in the timing of patient evaluations.

In mTBI patients who frequently exhibit normal brain images while maintaining good overall health and being discharged from the hospital, this issue is particularly significant. If these individuals hold demanding jobs that require high accuracy and rapid action, these disorders could lead to irreversible harm to society. Therefore, mTBI patients require special attention and screening through appropriate psychological tests to ensure they can safely return to work or engage in daily activities that necessitate focus and rapid responses, such as driving.

The findings of the study did not reveal a significant difference in the scores of the Wechsler memory subtest between the two groups of mTBI patients and healthy individuals. As we know, the hippocampus plays a crucial role in short-term or recent memory. In patients with mTBI, the force from the trauma may have impacted the more superficial areas of the brain, while the deeper regions, including the hippocampus, were less affected. This could explain the lack of change in Wechsler test scores in the present study. Moreover, a study conducted by de Freitas et al. showed that 24 hours after TBI, there were no significant differences between the two groups on the Visual Memory Test and the Digit Span Subtest from the Wechsler.[30]

The strengths of this study include its design as a cohort study of mTBI patients during the acute phase following trauma, as well as the administration of psychological tests during this period. However, the study had limitations, such as the small number of participants, the inability to examine the mid-term and long-term effects of mTBI on neurometabolites, and the lack of measurement of brain metabolites in other regions of the brain. Further studies are needed to assess neurometabolites in moderate and severe TBI patients across different brain regions with a larger sample size.

Conclusions

The results of the study indicated that the levels of brain metabolites in patients with mTBI shortly after the trauma do not differ from those of healthy individuals. Therefore, measuring brain metabolites during the acute phase following mTBI holds no predictive value for patient outcomes. However, psychological test results revealed that the speed of cognitive processing and executive function in the mTBI group was significantly lower than in healthy individuals. Consequently, it is recommended that this factor be considered during clinical and legal evaluations of patients. Further studies with larger sample sizes should be conducted on other brain regions, such as the thalamus, hippocampus, and gray matter. Additionally, we propose assessing the medium- and long-term effects of trauma on brain metabolites.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

mild Traumatic Brain Injury: mTBI;
Glasgow Coma scale: GCS;
Magnetic Resonance Spectroscopy: MRS;
N-acetyl Aspartate: NNA.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. This study has been approved by the ethics committee of Kashan University of Medical Sciences (ethical code: IR.KAUMS.MEDNT.REC.1400.186). In order to perform psychological tests, the consent was obtained from the studied subjects.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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