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ORIGINAL ARTICLE

Investigation of Early Diagnostic Value of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase Blood Levels in Minor Head Trauma in Turkey

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SUMMARY

Background: **The aim was to investigate the early diagnostic value of serum glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase (UCH-L1) levels in adults with minor head trauma (MHT) and whether it could be an alternative diagnostic method to computed tomography (CT). This is the first study with the combination of GFAP and UCH-L1 in the first 3 hours of MHT.**

Methods: **The study comprised 88 patients, 60 patients and 28 controls, who were evaluated as having MHT, were admitted to the emergency department of our hospital within the first 3 hours of the trauma and met the inclusion criteria. CT was performed on all patients. Serum GFAP and UCH-L1 levels were measured within the first 3 hours of the trauma.**

Results: **The median serum GFAP level was 1.07 ng/mL in the group with pathology on CT and 0.42 ng/mL in the group with no pathology on CT. The median serum UCH-L1 level was 0.40 ng/mL in the group with pathology on CT and 0.39 ng/mL in the group with no pathology on CT. A statistically significant difference was found between the serum GFAP levels of the CT (+) group and the CT (-) group ($p = 0.021$). GFAP levels were compared according to the CT (+) and CT (-) groups with a cutoff value of ≥ 1.56 ng/mL for GFAP, which had 50% sensitivity and 97.5% specificity. This was statistically significant ($p = 0.008$). It was found that the UCH-L1 level of the control group was lower than the UCH-L1 levels of the CT (+) and CT (-) groups, and this difference was found to be statistically significant ($p = 0.003$ and $p = 0.018$, respectively).**

Conclusions: **GFAP was found to be more specific than UCH-L1 in demonstrating the presence of intracranial pathology in patients with head trauma who were admitted to the emergency department in the first 3 hours after trauma.**

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INTRODUCTION

Traffic accidents, falls, accidents at home, work, and sports cause head injuries. Traffic accidents account for approximately 70% of head injuries and constitute the leading cause of death in 60% of those who die in acci-

dents [1]. Also, head trauma includes the majority of deaths in wars. For these reasons, it is a common situation encountered by emergency physicians. Approximately 56 - 60% of all trauma patients have mild or severe head trauma. In about 50% of deaths resulting from trauma, the cause of death is head trauma [2].

Computed tomography (CT) is the primary method used to diagnose, and CT scans are required in moderate and severe head trauma. The main indications for CT scanning in patients with minor head trauma (MHT) are a history of loss of consciousness, amnesia, vomiting twice or more, trauma findings in the area above the clavicle (contusion, abrasion, laceration, deformity, facial and skull bone findings), headache, skull fracture, neurologic deficit, coagulopathy, and seizure [3].

Physicians may be indecisive about using CT due to difficulties during the procedure. Such as exposure to radiation, cost, not being an easily accessible tool, requiring patient transfer for the procedure, lengthy procedure time, and immobility during shooting [4].

For this reason, studies on biochemical markers showing damage in brain cells have been conducted in recent years. One marker that has been investigated is glial fibrillary acidic protein (GFAP), and another is ubiquitin C-terminal hydrolase (UCH-L1). GFAP is a 50 kilodalton (kDa) monomeric intermediate-filament component of the astrocytic cytoskeleton almost exclusively expressed in the central nervous system (CNS) with a plasma half-life of 24 - 48 hours [5]. GFAP is released in CNS damage, thus indicating traumatic brain injuries. It is found in the structures of astroglial cells and is not located outside the CNS [6,7]. UCH-L1 is a proteolytically stable and abundant protein found almost exclusively in the cytoplasm of neurons. UCH-L1 is also specific to neurons as well as neurofilament light (NF-L), the smallest component of the axonal cytoskeleton. Previous studies have demonstrated that it is increased in serum after TBI [5-8]. It is not completely clear how these proteins leave the injured brain and enter the plasma. Blood-brain barrier (BBB) disruption or release independent of BBB integrity as well as passage through the newly discovered glymphatic system have been suggested as possible routes. These proteins are first released in the brain extracellular space before being transported to the cerebral spinal fluid and subsequently into serum [5].

This study aimed to investigate the early diagnostic efficacy of serum GFAP and UCH-L1 levels in adults with MHT and whether it could be an alternative diagnosis method to CT.

MATERIALS AND METHODS

This study is prospective clinical research with the approval of Sakarya University Faculty of Medicine Interventional Ethics Committee (Date: 06.10.2016, Number: 129) (Approval Number: 16214662/050.01.04/134). The study was conducted in Sakarya University Training and Research Hospital Emergency Medicine Clinic following the ethical principles of the World Medical Association Helsinki Declaration.

Study design

The study was performed on a total of 88 patients, comprising 60 patients and 28 healthy controls, who were admitted to the Emergency Medicine Clinic with MHT and met the inclusion criteria.

- Inclusion criteria: Among the patients who presented to the emergency medicine clinic of our hospital within the first 3 hours of injury due to head trauma, those with a Glasgow Coma Scale (GCS) of 14 - 15, indications for brain tomography (nausea-vomiting and trauma signs in the area above the clavicle, contusion, abrasion, laceration, with symptoms of deformity, facial and skull fractures), and aged over 18 years were included in the study.
- Exclusion criteria: Patients with known neurologic or psychiatric disease, patients with known spinal cord injury, patients with cancer, children, pregnant women, and patients who presented after the third hour were excluded from the study.

The patients' demographic data, trauma type, the time of admission to the emergency department after trauma, history of nausea and vomiting, the presence of amnesia, GCS levels, and information on CT interpretations were recorded. Patients were selected and evaluated very carefully, especially patients who applied to the emergency department after 3 hours who were not included in the study. Five-milliliter venous blood samples were taken from the patients and the control group to measure GFAP and UCH-L1 levels. Patients in the trauma group were also divided into two groups according to whether their CT had pathologic findings. Accordingly, those with pathologic findings in their CT (fracture, contusion, epidural hemorrhage, subdural hemorrhage, and subarachnoid hemorrhage) were considered as CT (+), and those without pathologic findings were considered as CT (-).

Laboratory analysis

The collected blood was centrifuged and stored at -80°C. In these sera, human GFAP and UCH-L1 kits (FineTest, China, www.fn-test.com) were used to determine GFAP and UCH-L1 levels. For this, samples and standards were loaded into designated wells. Then the appropriate antibody labeled with enzyme was added and incubated at 37°C for 30 minutes. The plates were washed five times, and a chromogen solution was added. Finally, stop solution was added to all wells and read in a microplate reader at 450 nm wavelength. A standard curve was drawn according to the concentrations of the standards, and optical density (OD) values were calculated accordingly.

Table 1. Distribution of demographic and clinical data by groups.

		Trauma group CT (+)	Trauma group CT (-)	Control	Total	p
		(n = 20)	(n = 40)	(n = 28)	(n = 88)	
		n (%)	n (%)	n (%)	n (%)	
Gender	female	3 (15.0)	14 (35.0)	12 (42.9)	29 (33.0)	0.119
	male	17 (85.0)	26 (65.0)	16 (57.1)	59 (67.0)	
Type of Trauma	fall	8 (40)	19 (47.5)	0 (0)	27 (30.7)	< 0.001
	IVTA *	10 (50)	14 (35)	0 (0)	24 (27.3)	
	assault	1 (5)	5 (12.5)	0 (0)	6 (6.8)	
	OVTA *	1 (5)	2 (5)	0 (0)	3 (3.4)	
	control	0 (0)	0 (0)	28 (100)	28 (31.8)	
Emergency Admission Time	1. hour	13 (65)	29 (72.5)	0 (0)	5 (8.3)	0.688
	2. hour	4 (20)	8 (20)	0 (0)	3 (5.0)	
	3. hour	3 (15)	3 (7.5)	0 (0)	2 (3.3)	
Nausea	(+)	12 (60)	16 (40)	0 (0)	28 (31.8)	< 0.001
	(-)	8 (40)	24 (60)	28 (100)	60 (68.2)	
Vomiting	(+)	5 (25)	1 (2.5)	0 (0)	6 (6.8)	0.003
	(-)	15 (75)	39 (97.5)	28 (100)	82 (93.2)	
Amnesia	(+)	14 (70)	0 (0)	0 (0)	14 (15.9)	< 0.001
	(-)	6 (30)	40 (100)	28 (100)	74 (84.1)	

Fisher-Freeman-Holton (Monte Carlo)/Kruskal Wallis H Test Post Hoc Test: Dunn's Test.
*** IVTA - In-Vehicle Traffic Accident, OVTA - Out-Vehicle Traffic Accident.**

Table 2. Distribution of GFAP and UCH-L1 levels by CT results.

		UCH-L1	GFAP	Age
		Med (min/max)	Med (min/max)	Med (min/max)
CT (+)	= I	0.40 (0.30/1.63)	1.07 (0.30/7.11)	47 (20/83)
CT (-)	= II	0.39 (0.30/1.13)	0.42 (0.30/1.97)	36 (18/87)
Control	= III	0.35 (0.30/0.45)	0.37 (0.30/1.80)	46 (20/69)
Total		0.38 (0.30/1.63)	0.41 (0.30/7.11)	40.5 (18/87)
p (General)		0.005	< 0.001	0.015
Pairwise comparisons	I→II	0.275	0.021	0.017
	I→III	0.003	<0.001	0.783
	II→III	0.018	0.023	0.019

Table 3. Examination of GFAP levels according to CT (+) and CT (-) groups.

	CT (+) and CT (-) groups				
	Sensitivity	Specificity	Cutoff value	AUC ± SH	p
GFAP	50%	97.5%	1.560	0.711 ± 0.081	0.008

ROC - (Receiver Operating Curve) Analysis (Honly & McNell - Youden index J), AUC - Area under the ROC curve, SD - Standard Deviation.

Table 4. Examination of GFAP and UCH-L1 levels according to CT (+) and Control groups.

	Between CT (+) and control groups				
	Sensitivity	**Specificity**	**Cutoff value**	**AUC ± SH**	**p**
UCH-L1	**65%**	**75%**	**0.385**	**0.722 ± 0.078**	**0.009**
GFAP	**90%**	**64.29%**	**0.375**	**0.802 ± 0.069**	**< 0.001**

ROC - (Receiver Operating Curve) Analysis (Honley & McNell - Youden index J), AUC - Area under the ROC curve, SD - Standard Deviation.

Table 5. Examination of GFAP and UCH-L1 levels according to CT (-) and Control groups.

	Between CT (-) and control groups				
	Sensitivity	**Specificity**	**Cutoff value**	**AUC ± SH**	**p**
UCH-L1	**77.5%**	**64.29%**	**0.360**	**0.685 ± 0.068**	**0.010**
GFAP	**85%**	**64.29%**	**0.375**	**0.682 ± 0.071**	**0.011**

ROC - (Receiver Operating Curve) Analysis (Honley & McNel - Youden index J), AUC - Area under the ROC curve, SD - Standard Deviation.

Statistical analysis

The SPSS 24.0 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) program was used to analyze variables. The compliance of the data to normal distribution was evaluated using the Shapiro-Wilk test. According to quantitative data, the Kruskal-Wallis H test was used to compare multiple independent groups using the Monte Carlo simulation technique. Dunn's test was used for post hoc analyses. The Fisher-Freeman-Holton test was tested using Monte Carlo simulation for comparing categorical variables with each other. The sensitivity and specificity of the relationship between the classification of the cutoff value calculated according to the variables and the accurate classification of the groups were examined and expressed using receiver operating curve (ROC) analysis. Quantitative variables are shown as median and range (Maximum-Minimum) in the tables, and categorical variables as percentage "%." Variables were examined at a 95% confidence level, and those with a p-value of less than 0.05 were considered significant.

RESULTS

Sixty of the 88 patients included in the study had MHT, 20 were CT (+), and 40 were CT (-). The data regarding the gender, trauma type, duration after trauma to admission to the emergency department, history of nausea and vomiting, whether there was amnesia, and the comparison of variables according to the groups is presented in Table 1.

Fifty-nine (67%) of the patients included in the study were male and 29 (33%) were female. The most common cause of trauma was falling. A statistically significant difference was found between the groups and the types of trauma ($p < 0.001$). In the CT (+) group, 13 (65%) presented to the emergency department in the first hour, four (20%) in the second hour, and three (15%) in the third hour after trauma. CT was performed on all patients. In the CT (+) group, three (15%) patients had fractures, two (10%) patients had a contusion, five (25%) had an epidural hemorrhage, four (20%) had subdural bleeding, and six had SAH (30%). It was observed that 12 of the patients (60%) had a GCS of 15, and eight (40%) had a GCS of 14.

Amnesia was observed in most patients (70%) in the CT (+) group, nausea was observed in most patients (40%) in the CT (-) group; there was a statistically significant difference between the variables of nausea, vomiting, and amnesia between the groups ($p < 0.001$, $p = 0.003$, and $p < 0.001$, respectively).

The median serum GFAP level was 1.07 (range 0.30 - 7.11) ng/mL in the CT (+) group, and the median serum GFAP level was 0.42 (range, 0.30 - 1.97) ng/mL in the CT (-) group. A statistically significant difference was found between the serum GFAP levels of the CT (+) group and the CT (-) group ($p = 0.021$). When paired comparisons were made between the groups, a statistically significant difference was found ($p = 0.021$, $p < 0.001$, and $p = 0.023$, respectively) (Table 2).

The median serum UCH-L1 level was 0.40 (range, 0.30 - 1.63) ng/mL in the CT (+) group, and 0.39 (range, 0.30 - 1.13) ng/mL in the CT (-) group. No statistically significant difference was found between the groups ($p = 0.275$). When paired comparisons were made between the groups, the UCH-L1 level of the control group was lower than in the CT (+) and CT (-) groups, and this dif-

ference was found to be statistically significant ($p = 0.003$ and $p = 0.018$, respectively) (Table 2).

When GFAP levels were compared according to the CT (+) and CT (-) groups, it was observed that those with a cutoff value of ≥ 1.56 ng/mL for GFAP had 50% sensitivity and 97.5% specificity, and this was statistically significant ($p = 0.008$) (Table 3).

When GFAP levels were compared with the CT (+) and control groups, it was observed that those with a cutoff value of ≥ 0.375 ng/mL for GFAP were CT (+) with 90% sensitivity and 64.29% specificity, and this was found to be statistically significant ($p < 0.001$). When UCH-L1 levels were compared with the CT (+) and control groups, those with a cutoff value of ≥ 0.385 ng/mL for UCH-L1 were observed to be CT (+) with 65% sensitivity and 75% specificity, and this was statistically significant ($p = 0.009$) (Table 4).

When GFAP levels were compared according to the CT (-) and control groups, it was observed that those with a cutoff value of ≥ 0.375 ng/mL and above for GFAP had 85% sensitivity and 64.29% specificity CT (-), and this was statistically significant ($p = 0.011$). When UCH-L1 levels were compared according to the CT (-) and control groups, those with cutoff values of ≥ 0.360 ng/mL were observed to be CT (-) with 77.5% sensitivity 64.29% specificity, and this was statistically significant ($p = 0.010$) (Table 5).

When the laboratory data (GFAP and UCH-L1 results) of the groups were examined, no statistically significant difference was found between the emergency department presentation hours and the laboratory data ($p > 0.05$).

DISCUSSION

TBI constitutes the majority (80%) of head injuries. Traffic accidents are the most common cause of TBI in the general population, followed by falls, but TBI due to falls takes first place in the elderly [1]. Karasu et al. evaluated 430 patients who were hospitalized out of 1,787 patients who were admitted to the emergency department due to head trauma throughout 2006. It was shown that the two most common causes of TBI were falling from height (40%) and traffic accidents (37%) [9]. In our study, falls (30.7%) were the most common cause of TBI.

It has been stated in the literature that men have more TBI than women [10]. In our study, it was found that men (67%) had more TBI. Many studies have shown that most (73 - 93%) patients with head injuries present to healthcare facilities within the first 6 hours. In our study, we observed that most patients (79.5%) presented to the emergency department in the first hour.

It has been shown that the most common symptoms during the admission of patients with head trauma include nausea, vomiting, and amnesia [11,12]. Harad et al. reported 18% of patients with MHT had a history of nausea, vomiting, and amnesia, 18.4% of 686 patients by Stein et al., and Wang et al. recorded 37.4% in their study. Simon et al. showed that 16% had pathology in CT in their study [11-14]. The researchers argued that CT was necessary, emphasizing that the possibility of intracranial pathology was higher in patients with MHT, nausea, vomiting history, and amnesia. In our study, especially in the presence of a history of vomiting and amnesia, CT (+) was seen in 70% of patients, compatible with the literature.

There are many parameters to performing CT in patients with MHT. The most important of these is the GCS score [15]. In the literature, authors supported cranial CT in patients with a GCS score of 14 because the incidence of intracranial pathology was 13 - 18%. Conversely, there are significant differences of opinion about whether CT should be performed in patients with a GCS score of 15 [16]. Regarding the subject, in patients with MHT with a GCS score of 14 - 15 according to New Orleans and Canada criteria, recurrent vomiting, age 65 years, and trauma findings in the area above the clavicle (contusion, abrasion, laceration, deformity, facial and skull fracture findings), presence of clinical findings of skull base fracture, coagulopathy, dangerous trauma mechanism, and any findings of focal neurologic deficit, cranial CT is recommended [3,15]. Based on all these suggestions, in our study, patients with GCS scores of 14 and 15 with recurrent vomiting, dangerous trauma mechanism, and trauma in the area above the clavicle were evaluated using CT.

Boran et al. performed CT scans in patients with GCS scores of 15 in their study of 371 patients and found pathology in 9.2% [16]. Miller et al. found that the GCS of 114 of 133 patients with head trauma cases was 15 (85.7%), 12 (9%) were 14, and seven (5.3%) patients were 13. The authors found that 71.4% of patients with a GCS score of 13, 33.3% of patients with a GCS score of 14, and 9.6% of patients with a GCS score of 15 had intracranial pathology on CT [17]. In our study, in our 88-patient case series, 60 patients with head trauma underwent CT scans, two (3.33%) had a contusion, three had fractures (5%), four (6.66%) had subdural bleeding, five (8.33%) had epidural bleeding, and six (10%) had subarachnoid bleeding. Pathologic CT results were detected in 20 (33.33%) patients.

Missler et al. found that serum GFAP levels were high in patients with severe head trauma in their study. Serum GFAP levels were found to be the highest in those who presented within the first 3 hours after injury, and it was shown that serum GFAP levels were elevated in 56% of samples taken at 4 - 6 hours and in only 10% of samples taken 6 hours later. It has been shown that serum GFAP levels gradually decrease after the first 6 hours following MHT [18]. Lumpkins et al. showed a significant decrease in serum GFAP levels from the second day in their study in adults with severe head trauma. They found that high GFAP levels that continued until the second day were significantly associated with death [19]. Wiesmann et al., in their study on 60 patients with GCS scores ranging from 3 to 15, found that

serum GFAP levels were significantly higher in the first 6 hours, and there was a significant decrease in serum GFAP levels in blood taken after the sixth hour [20]. Zurek et al. stated that serum GFAP levels were higher after TBI in patients associated with mortality and remained elevated for a few days in their studies involving patients with severe head trauma [21]. In their experimental study, Cikriklar et al. observed that there was a direct proportional relationship between serum GFAP levels and the severity of the trauma and found that as the severity of trauma increased, serum GFAP levels also increased [22]. It has been shown that serum GFAP levels increase in the first 6 hours in patients with severe head trauma (GCS 3 - 8); they start to decrease gradually after the sixth hour and decrease rapidly after the second day. Most studies on GFAP in the literature cover severe head trauma and the first six hours after trauma and beyond; our analysis covers patients with MHT and the first 3 hours after trauma. Our study determined that serum GFAP levels increased in the early period, and serum GFAP values of those with CT (+) were higher than those who were CT (-) and the controls. These results are compatible with the literature and show that serum GFAP can also be used for the early detection of traumatic brain injury.

Takala et al. showed that serum UCH-L1 increased on the first day and decreased after the second day [23]. Kobeissy et al., in their study in rats, found that UCH-L1 increased for 48 hours after the trauma and then decreased [24]. Papa et al. found that serum UCH-L1 increased rapidly after injury, peaked in 8 hours, and regressed within 48 hours [25]. In our study, UCH-L1 levels were examined in patients who presented to the emergency department within the first 3 hours after MHT, and it was seen that UCH-L1 could increase in the first 3 hours. Still, this increase failed to distinguish between the CT (+) and CT (-) groups.

Papa et al. also determined intracranial pathology with 95% specificity in those with a serum GFAP cutoff value of ≥ 0.80 ng/mL and serum UCH-L1 cutoff value of ≥ 0.77 ng/mL had 95% specificity [25]. In our study, among the CT (+) and control groups after MHT, those with a serum GFAP cutoff value of ≥ 0.375 ng/mL had 64.29% specificity, and patients with a serum UCH-L1 cutoff value of ≥ 0.385 ng/mL had 75% specificity for being CT (+), that is, they had an intracranial pathology. Those with serum GFAP cutoff values of ≥ 1.56 ng/mL were found to be CT (+) with 97.5% specificity, and for serum UCH-L1, patients admitted in the first 3 hours, CT (+) and CT (-). No substantial cutoff value was found that could distinguish the groups from each other. It was concluded that the measurement of serum GFAP level was effective in demonstrating an intracranial pathology in patients with MHT admitted to the emergency department in the first 3 hours after trauma but serum UCH-L1 blood level measurements were insufficient. The most significant limitation of this study is the sample size. Although our study covered nine months, the sample size was small compared with other studies. The most important reason for this was that many patients had to be excluded from the study due to patients who applied later than 3 hours after trauma. On the other hand, there is a need for new studies with a larger number of patients, as this is the first study to deal with the combination of GFAP and UCH-L1 in the first 3 hours of head trauma.

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