Medico-legal application of ubiquitin C-terminal hydrolase L1 in mild and moderate head injured patients

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ABSTRACT

Introduction: Head trauma is considered a frequent cause of death and disability in Egypt and worldwide. Evaluation of head injured patient is required in different forensic settings. Recently, biomarkers have been introduced to predict outcomes of traumatic head injury. Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is one of the novel biomarkers with neuronal specific components. Thus, the current study aimed to evaluate the medico-legal application of UCH-L1 as a prognostic marker in mild and moderate head injured patients. The current study was conducted on forty-five adult subjects during the period from June 2018 to December 2018. They were divided into: 15 mild head injured patients (group I), 15 moderate head injured patients (group II) and 15 healthy subjects served as controls (group III). All participants were subjected to history taking, clinical examination, head computed tomography scan, and estimation of UCH-L1 concentration. Results: UCH-L1 concentration was significantly higher in group I and II compared to group III, moreover it was significantly higher in group II compared to group I. Significant positive correlations were observed between UCH-L1 concentration and each of hospitalization period and duration of post-traumatic amnesia in all head injured patients. The median concentration of UCH-L1 in patients who developed complications (11.90 ng/ml) was significantly higher than in patients who didn’t have complications (0.04 ng/ml). UCH-L1 could predict complications at cut off value > 0.2 ng/ml. Conclusions: Serum UCH-L1 could be useful for forensic experts to establish cause-effect relationship between poor outcome and trauma in head injured patients.

KEYWORDS: Head injury, ubiquitin C-terminal hydrolase-L1, outcome, prediction, biomarkers.

ABBREVIATIONS:
INTRODUCTION

Traumatic head injury (THI) represents one of the most important causes of morbidity, mortality, and resource consumption in Egypt and other countries (Atwa et al. 2017; Kandil et al. 2017). THI refers to physical damage to any of the head structures including scalp, skull, meninges, and brain caused by external mechanical force (Onwuchekwa and Echem 2018). This force may be direct impact, penetration by a projectile or even rapid acceleration/deceleration or blast waves (Mckee and Daneshvar 2015).

Cases of THI require meticulous forensic and clinical evaluation. In medico-legal practice, it is important to link between outcome and trauma for legal purposes in addition to compensation and social support. Moreover, THI requires accurate assessment in case of malpractice claims (John 2011; Lee et al. 2012). For neurosurgeons, early detection of patients with poor prognosis is essential for better management and outcome (El-Sarnagawy et al. 2018).

Several prognostic factors were proposed to predict the outcome in head injured patients such as initial neurological examination including Glasgow Coma Scale (GCS) and head computed tomography (CT) findings. However, neurological examination within the first 24 hours of the injury might be an inaccurate predictor due to sedation, analgesia, poor patient cooperation, possible associated intoxication with one of the substances of dependence, and physiological circadian rhythmicity (La Rosa et al. 2004; Rundhaug et al. 2015; Yue et al. 2017). In addition, CT findings provide only moderate sensitivity and specificity for prognosis (Goyal et al. 2013). Accordingly, there is an urgent need for development of other modalities to diagnose and predict the outcome in head injured patients for forensic and clinical utility.

One of the novel biomarkers with neural specific components is ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1) (Bishop et al. 2016). UCH-L1 constitutes about 5-10% of cytoplasmic neuronal proteins making it an important neuronal histological marker. Additionally, it is highly important for neuronal cell survival and axonal transport (Shahjouei et al. 2018). UCH-L1 is a stable protein that can be released from neurons and detected in both cerebrospinal fluid and systemic circulation after THI (Liu et al. 2010). It can be detected within 1 hour after injury, reaches its peak within 8 hours and declines rapidly over 48 hours (Papa et al. 2016). So it could be proposed as a suitable marker for early prediction of prognosis in mild and moderate traumatic head injured patients.

SUBJECTS AND METHODS

The current cohort prospective study was conducted on forty-five subjects who were divided into three groups; group I included fifteen mild head injured patients, group II included fifteen moderate head injured patients, and group III included fifteen healthy volunteers served as controls who matched for age and sex with the previous two groups.

Severity of THI was divided into mild and moderate according to GCS at time of presentation; mild injury when GCS is 13 or above and moderate injury when GCS is 9 to 12 (Naveed et al. 2010 and Mehdi et al. 2013).
Inclusion criteria:

- Patients with THI aged 18-50 years who presented within a period ranging between more than 1 hour and up to 24 hours after trauma
- Initial GCS of 9-15 as performed by the principal investigator
- Different causes of THI including acceleration or deceleration injury that was either self-reported or witnessed

Exclusion criteria:

- Cases presented after 24 hours of head injury
- History of previous neurological illness or psychiatric impairment
- Presence of other associated trauma
- Patients who needed surgical intervention
- Patients with tumors such as pancreatic, colorectal, and invasive breast cancers

Socio-demographic data (age, sex, marital status, residence, and occupation) and medical history (pre-existing chronic diseases and drug intake) were obtained from all participants. Medico-legal aspects of trauma (cause and manner of trauma, pre-hospitalization period, treatment received, duration of post-traumatic amnesia, and hospitalization period) and patient outcome either survivors (with or without complications) or non-survivors were reported for all traumatic head injured patients. Clinical examination of different body systems including head, neck, chest, abdomen, and extremities was performed. Level of consciousness was assessed by GCS according to McKeel and Daneshvar (2015) and head CT scan was performed for each patient at time of admission. A venous blood sample was obtained on admission from each participant for estimation of UCH-L1 concentration. Determination of UCH-L1 concentration was done by Sandwich-ELISA technique using human UCH-L1 Kit (Catalog No: MBS452467) supplied by MyBiosource, San Diego, USA. Patients with THI were followed up 6 months after trauma to detect complications.

The study was performed after the approval of the institution research ethics committee (Approval Number: 32333/05/18). A written informed consent was obtained from each patient or his/her guardians (if the patient was unable to participate in the consent process) after receiving detailed information about the scope of the study. Confidentiality of the data was maintained by making code number for each patient.

Statistical analysis:

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22. For quantitative data, the Shapiro-Wilk test for normality was performed. For data that followed normal distribution, values were expressed as mean ± standard deviation. Comparisons between groups were carried out using independent samples T-test (for two groups) or one-way ANOVA (for three or more groups). For data that did not follow normal distribution, median, and interquartile range (IQR) expressed as 25th-75th percentiles were assessed. Mann-Whitney test was used to make comparisons between two groups. Correlations between numerical variables were tested using either Pearson’s or Spearman’s rank-order correlation. For qualitative data, the variables were summarized as frequencies (count and percentage). Pearson’s Chi square test for independence and Fisher’s exact test or
Fisher-Freeman-Halton exact test were used to examine association between two categorical variables as appropriate. Univariate and multivariate multiple regression analyses were performed to examine the effect of potential factors on UCH-L1 concentration. Analysis of the relation between true-positive and false-positive results for UCH-L1 concentration as a predictor of delayed complications was done by using the receiving operating characteristic (ROC) curve. The area under the curve (AUC) was classified as follows: 0.90-1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair, and 0.60-0.70 = poor. Significance was adopted at p < 0.05 for interpretation of test results.

RESULTS

The current study enrolled 15 mild head injured patients (group I), 15 moderate head injured patients (group II), and 15 healthy subjects served as controls (group III). Table 1 shows socio-demographic characteristics of the studied participants. Statistical analysis revealed no significant difference between the three studied groups regarding any of the socio-demographic data.

Medico-legal aspects of trauma are illustrated in Table 2 where road traffic accident was the most frequent reported cause of trauma (36.7%); the majority of cases were injured accidentally (66.7%) and the mean value of pre-hospitalization period was 12.7 ± 7.3 hours for all studied head injured patients with no significant difference between group I and group II regarding cause and manner of trauma and pre-hospitalization period. In contrast, the median value of the period of post-traumatic amnesia in group II (37.4 ± 11.7 hours) was significantly higher compared to that of group I (13.9 ± 7.5 hours). The median value of hospitalization period was 5.4 ± 3.9 days for all head injured patients with significant difference between group I and II. Glasgow Coma Scale of the 30 head injured cases ranged from 12 to 15 with a median value of 13. Mild head injured patients presented with GCS ranging between 13 and 15 while moderate head injured patients presented with GCS of 12; this could justify that the median GCS value for all patients (30 patients) was 13.

Table 3 shows the distribution of head injuries in all studied head injured patients. Scalp injuries, skull fractures, meningeal hemorrhages, and brain injuries were observed in 50%, 43.3%, 60%, and 6.7% of all patients respectively.

In the current study, 60% of patients presented with multiple head injuries with no significant difference between group I and group II. Table 4 shows that there was significant difference between the three studied groups regarding UCH-L1 concentration. Concentration of UCH-L1 in each of group I and group II was significantly higher compared to the control group. Moreover, UCH-L1 concentration in group II was significantly higher in comparison to its value in group I.

Regarding outcome, there were no reported cases of death among the studied head injured patients. Based on follow-up clinical evaluation 6 months after trauma, table 5 reveals that complications were present in 13.3% and 93.3% of patients in group I and group II respectively with significant difference between group I and II. Post-traumatic neurosis was the most frequent reported complications (40%) of all studied patients followed by personality changes (6.7%), then cranial nerve injuries and infection were equally distributed (3.3% each).
Statistical analysis revealed that there was no significant correlation between UCH-L1 concentration and age in all studied groups. Additionally, there was no significant correlation between UCH-L1 concentration and pre-hospitalization period in all studied head injured patients. On the other hand, there was strong positive significant correlation between UCH-L1 concentration and each of the severity of head trauma, hospitalization period, and post-traumatic amnesia in all head injured patients (Table 6).

Table 7 demonstrates that there was no significant difference regarding UCH-L1 concentration between cases presented with single head injury and cases presented with multiple head injuries (in the present study, multiple head injuries mean more than one injury even if they were caused by only one trauma whereas single head injury means only one injury). On the other hand, UCH-L1 concentration was significantly higher in cases developed complications than those without complications.

Univariate analysis demonstrated that sex and GCS can affect serum concentration of UCH-L1. Given that, sex and GCS were entered as independent variables in a multivariate regression analysis. The multivariate analysis revealed that GCS, when sex was adjusted, impacted significantly UCH-L1 concentration ($p < 0.001$). Decrease in GCS by one unit was associated with a significant increase in UCH-L1 concentration by 4.077 units as shown in Table 8.

Using ROC curve analysis, the current study revealed that UCH-L1 was significantly valid to discriminate cases of head injuries that will develop complications ($p$-value $< 0.001$). It showed excellent performance ($AUC = 0.948$) with 88.2% sensitivity and 100% specificity at cut off > 0.2 ng/ml as illustrated in Figure 1.
Table 1 Socio-demographic data of the three studied groups (n = 45)

| Variables          | Groups                      | Test of significance |
|--------------------|-----------------------------|----------------------|
|                    | Group I (n = 15)            | Group II (n = 15)    | Group III (n = 15) | Total (n = 45) | Test statistic | p-value |
| Age (years) Range  | 20.0 - 50.0                 | 18.0 - 50.0          | 21.0 - 50.0        | 18.0 - 50.0    | F = 1.037      | 0.369   |
| Age (years) Mean ± SD | 32.9 ± 10.0                | 31.7 ± 11.8          | 28.7 ± 6.5         | 31.1 ± 9.7     |                |         |
| Sex Male n (%)     | 11 (73.3%)                  | 13 (86.7%)           | 10 (66.7%)         | (75.6%)        |                |         |
| Sex Female n (%)   | 4 (26.7%)                   | 2 (13.3%)            | 5 (33.3%)          | 11             |                | 1.706   |
| Sex Female n (%)   | 4 (26.7%)                   | 2 (13.3%)            | 5 (33.3%)          | 11             |                | 0.566   |
| Marital Status     | 10 (66.7%)                  | 10 (66.7%)           | 6 (40%)            | 26             |                |         |
| Marital Status     | 5 (33.3%)                   | 5 (33.3%)            | 9 (60%)            | (42.2%)        |                |         |
| Residence Urban n (%) | 10 (66.7%)             | 10 (66.7%)           | 12 (80%)           | 32             |                | 0.233   |
| Residence Rural n (%) | 5 (33.3%)               | 5 (33.3%)            | 3 (20%)            | 13             |                | 0.770   |
| Residence Rural n (%) | 5 (33.3%)               | 5 (33.3%)            | 3 (20%)            | 13             |                |         |
| Residence Urban n (%) | 10 (66.7%)             | 10 (66.7%)           | 12 (80%)           | 32             |                |         |
| Residence Rural n (%) | 5 (33.3%)               | 5 (33.3%)            | 3 (20%)            | 13             |                |         |
| Occupation Employer n (%) | 2 (13.3%)             | 4 (26.7%)            | 4 (26.7%)          | (22.2%)        |                |         |
| Occupation Housewife n (%) | 2 (13.3%)             | 2 (13.3%)            | 2 (13.3%)          | 6 (13.3%)      |                |         |
| Occupation Unemployed n (%) | 1 (6.7%)              | 2 (13.3%)            | 1 (6.7%)           | 4 (8.9%)       |                | 0.526   |
| Occupation Student n (%) | 1 (6.7%)               | 4 (26.7%)            | 4 (26.7%)          | 9 (20.0%)      |                | 7.723   |
| Occupation Worker n (%) | 9 (60.0%)               | 3 (20.0%)            | 4 (26.7%)          | (35.6%)        |                |         |

n: number; SD: standard deviation; F: One-way ANOVA; X²ChS: Pearson’s Chi square test; X²FFH: Fisher-Freeman-Halton exact test; T: Independent samples T-test

Group I: Mild head injury group
Group II: Moderate head injury group
Group III: Control group
Table 2 Medico-legal aspects of trauma in all studied head injured patients (n = 30)

| Variables                        | Group I (n = 15) | Group II (n = 15) | Total (n = 30) | Tests of significance |
|----------------------------------|------------------|-------------------|----------------|-----------------------|
|                                  |                  |                   |                | Test statistic        | *P*                |
| Cause of trauma                  |                  |                   |                |                       |                   |
| Road traffic accident n (%)      | 7 (46.7%)        | 4 (26.7%)         | 11 (36.7%)     |                       |                   |
| Falls n (%)                      | 5 (33.3%)        | 4 (26.7%)         | 9 (30.0%)      | X²_{FFH} = 3.555      | 0.368             |
| Blunt force trauma to the head n (%) | 1 (6.7%)        | 5 (33.3%)         | 6 (20.0%)      |                       |                   |
| Sharp force trauma to the head n (%) | 2 (13.3%)       | 2 (13.3%)         | 4 (13.3%)      |                       |                   |
| Manner of trauma                 |                  |                   |                |                       |                   |
| Accidental n (%)                 | 12 (80.0%)       | 8 (53.3%)         | 20 (66.7%)     | X²_{ChS} = 2.400      | 0.121             |
| Non accidental n (%)             | 3 (20.0%)        | 7 (46.7%)         | 10 (33.3%)     |                       |                   |
| Pre-hospitalization period (hours) |                |                   |                |                       |                   |
| Range                           | 1.0 - 23.3       | 4.3 - 24.0        | 1.0 - 24.0     | T = 0.331             | 0.743             |
| Mean ± SD                       | 12.3 ± 8.0       | 13.2 ± 6.9        | 12.7 ± 7.3     |                       |                   |
| Post-traumatic amnesia (hours)   |                  |                   |                |                       |                   |
| Range                           | 3.0 - 23.0       | 24.0 - 48.0       | 3.0 - 48.0     | T = 6.533             | < 0.001*          |
| Mean ± SD                       | 13.9 ± 7.5       | 37.4 ± 11.7       | 25.6 ± 15.4    |                       |                   |
| Hospitalization period (days)    |                  |                   |                |                       |                   |
| Range                           | 2.0 - 3.0        | 2.0 - 14.0        | 2.0 - 14.0     | T = 6.087             | < 0.001*          |
| Mean ± SD                       | 2.5 ± 0.5        | 8.3 ± 3.7         | 5.4 ± 3.9      |                       |                   |

n: number; X²_{FFH}: Fisher-Freeman-Halton exact test; X²_{ChS}: Pearson’s Chi square test; T: Independent samples T-test

Group I: Mild head injury group
Group II: Moderate head injury group
Table 3 Distribution of head injuries in all head injured patients (n = 30)

| Types of head injuries          | Head injured patients |       |   |
|---------------------------------|-----------------------|-------|---|
|                                 | n (n = 30)            | %     |
| Scalp wounds                    | 15                    | 50.0% |
| Scalp contusions                | 8                     | 26.7% |
| Cut wounds                      | 7                     | 23.3% |
| Contused wounds                 | 2                     | 6.7%  |
| Skull fractures                  | 13                    | 43.3% |
| Vault fractures                  | 11                    | 36.7% |
| Base fractures                   | 4                     | 13.3% |
| Meningeal hemorrhages            | 18                    | 60.0% |
| Epidural hemorrhage              | 7                     | 23.3% |
| Subdural hemorrhage              | 7                     | 23.3% |
| Subarachnoid hemorrhage          | 9                     | 30.0% |
| Brain injuries                   | 2                     | 6.7%  |
| Brain contusion                  | 1                     | 3.3%  |
| Pneumocephalus                   | 1                     | 3.3%  |

n: number

Table 4 Ubiquitin C-terminal hydrolase L1 concentration in the three studied groups (n = 45)

| Ubiquitin C-terminal hydrolase L1 concentration | Groups | Tests of significance |       |   |
|-------------------------------------------------|--------|-----------------------|-------|---|
| Group I (n = 15)                                | Group II (n = 15) | Group III (n = 15) | T-test/One way ANOVA | p     |
| Range (ng/ml)                                   | 0.10 - 0.20 | 2.60 - 20.10 | 0.03 – 0.04 | F=18.607 <0.001* |
| Mean ± SD                                       | 0.14 ± 0.05 | 12.16 ± 4.51 | 0.03 ± 0.003 | P1<0.001* P2<0.001* P3<0.001* |

n: number; SD: standard deviation; F: One-way ANOVA; ng/ml: nanogram/millilitre; *significant at p<0.05; T: Independent samples T-test
P1: Comparison between group I and group II
P2: Comparison between group I and group III
P3: Comparison between group II and group III
Table 5 Complications among head injured patients (n = 30)

| Complications               | Groups                        | Test of significance |
|-----------------------------|-------------------------------|----------------------|
|                             | Group I (n = 15) | Group II (n = 15) | Total (n = 30) | Test statistic |
| Absent n (%)                | 13 (86.7%)     | 1 (6.7%)      | 14 (46.7%) | X^2_{ChS} =<0.001* |
| Present n (%)               | 2 (13.3%)      | 14 (93.3%)    | 16 (53.3%) | 22.941 |
| Cranial nerve injury n (%)  | 1 (6.7%)       | 0 (0.0%)      | 1 (3.3%)  | X^2_{FFH} =<0.001* |
| Infection n (%)             | 0 (0.0%)       | 1 (6.7%)      | 1 (3.3%)  | 28.150 |
| Personality changes n (%)   | 0 (0.0%)       | 2 (13.3%)     | 2 (6.7%)  |                   |
| Post traumatic neurosis n (%) | 1 (6.7%)     | 11 (73.3%)    | 12 (40.0%)|                   |

n: number; X^2_{ChS}: Pearson’s Chi square test; X^2_{FFH}: Fisher-Freeman-Halton exact test; *significant at p < 0.05

Group I: Mild head injury group
Group II: Moderate head injury group

Table 6 Correlation of age, pre-hospitalization period, severity, hospitalization period and post-traumatic amnesia with ubiquitin C-terminal hydrolase L1 concentration in the studied groups (n = 45)

| Variables               | All | Group I (n = 15) | Group II (n = 15) | Group III (n = 15) |
|-------------------------|-----|-----------------|-------------------|---------------------|
| Age (years)             | r_s | 0.122           | 0.174             | 0.165               | 0.000               |
|                         | n   | 45              | 15                | 15                  | 15                  |
| Pre-hospitalization     | r_s | -0.191          | -0.853            | -0.029              | —                   |
| period (hours)          | P   | 0.313           | <0.001*           | 0.919               | —                   |
|                         | n   | 30              | 15                | 15                  | —                   |
| Severity                | r_s | 0.960           | —                 | —                   | —                   |
|                         | P   | <0.001*         | —                 | —                   | —                   |
|                         | n   | 30              | —                 | —                   | —                   |
| Hospitalization period  | r_s | 0.957           | —                 | —                   | —                   |
| (days)                  | P   | <0.001*         | —                 | —                   | —                   |
|                         | n   | 30              | —                 | —                   | —                   |
| Post-traumatic amnesia  | r_s | 0.804           | —                 | —                   | —                   |
| (hours)                 | P   | <0.001*         | —                 | —                   | —                   |
|                         | n   | 30              | —                 | —                   | —                   |

n: number; rs: Spearman’s correlation coefficient; * significant at p < 0.05

Group I: Mild head injury group
Group II: Moderate head injury group
Group III: Control group
Table 7 Ubiquitin C-terminal hydrolase L1 concentration in relation to number of injuries and occurrence of complications in head injured patients (n = 30)

| Variables       | Ubiquitin C-terminal hydrolase L1 Concentration (ng/ml) | Mann-Whitney test |
|-----------------|--------------------------------------------------------|-------------------|
|                 | Range        | Median       | IQR        | Mean ranks | Z    | p    |
| Number of injuries | Single      | 0.10 - 20.1 | 1.40       | 0.15 - 11.15 | 15.7 | 0.108 | 0.914 |
|                 | Multiple     | 0.10 - 15.80 | 5.25       | 0.10 - 11.90 | 15.4 | -     |      |
| Complications   | Absent       | 0.03 - 0.20 | 0.04       | 0.03 - 0.10 | 14.9 | 5.396 | <0.001* |
|                 | Present      | 0.10 - 20.10 | 11.90      | 6.90 - 15.40 | 36.3 | -     |      |

IQR: interquartile range; Z: test statistic of Mann-Whitney test; ng/ml: nanogram/milliliter; *significant at p < 0.05

Table 8 Multiple regression analysis for factors affecting Ubiquitin C-terminal hydrolase L1 concentration

|                | Univariate | Multivariate |
|----------------|------------|--------------|
|                | B          | SE          | T     | P    | 95.0% C.I. for B | B          | SE          | T     | P    | 95.0% C.I. for B |
| Age (years)    | 0.052      | 0.099       | 0.523 | 0.604 | -0.15 to 0.25.   | 0.052      | 0.099       | 0.523 | 0.604 | -1.28 to 2.87   |
| Sex (female)   | -3.604     | 1.905       | 1.892 | 0.065 | -7.45 to 0.24    | -3.604     | 1.905       | 1.892 | 0.065 | -4.80 to 3.36   |
| GCS            | -3.973     | 0.330       | 12.045 | <0.001* | -4.64 to 3.31   | -3.973     | 0.330       | 12.045 | <0.001* | -4.80 to 3.36   |
| Number of injuries Pre-hospitalization period (hours) | 0.569 | 2.603 | 0.219 | 0.828 | -4.76 to 5.90   | -0.469     | 0.177       | 0.387 | 0.702 | -0.29 to 0.43   |

B: unstandardized regression coefficient; C.I.: confidence interval; GCS: Glasgow Coma Scale; *significant at p < 0.05
**DISCUSSION**

In the current study, there was no significant difference between the three studied groups regarding socio-demographic data. However, studying such data is very important as head injuries could affect the ability to return to work and money earning and may lead to relational stress and family disruption. In addition, the age and factors related to the living situations of the patients may affect the speed and degree of recovery (Maas et al. 2010).

Past history was taken from each participant to exclude pre-existing diseases or drug intake that may influence GCS or UCH-L1 concentration as hepatic encephalopathy, diabetic coma, renal failure, previous stroke, and CNS depressants (Posti et al. 2016; Singh et al., 2018). Head injury may occur in isolation as well as in combination with other injuries (Junaid et al. 2016). Therefore, in this study physical examination of different body systems was performed for all participants to rule out any associated trauma.

Road traffic accidents and falls were reported as the most frequently encountered causes of head injury in the present study (36.7% and 30% respectively). Similar findings were obtained by Al-kuwaiti et al. (2012) in United Arab Emirates however they reported a higher percentage for road traffic accidents (67.1%) and a lower percentage for falling from height (11.9%). In a Turkish study conducted by Aras et al. (2016), falling from height and road traffic accidents were responsible for 59% and 18% of their studied head injured cases respectively. In Egypt, overcrowding and lack of proper strategy for prevention of combination with other injuries (Junaid et al. 2016). Therefore, in this study physical examination of different body systems was performed for all participants to rule out any associated trauma.

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road traffic accidents, contribute to make Egypt one of the highest world’s road traffic accidents rate (El Bakash et al. 2016).

Regarding the manner of head injury, the majority of the studied cases were injured accidently (66.7%) while non-accidental injuries were reported in 33.3%. These results are in partial agreement with those of Abo El-Noor et al. (2017) who reported that most of the studied head injured patients (86.67%) were injured accidentally versus 13.33% injured non-accidentally.

The mean value of pre-hospitalization period reported in the present study was 12.7 hours with no significant difference between group I and II (p-value = 0.743). Pre-hospitalization period is highly determined by transportation facilities and rapidity of seeking medical care (Vaca et al. 2018).

Duration of post traumatic amnesia is considered the most sensitive index determining the degree of diffuse axonal injury and can predict the severity and outcome of traumatic brain injury (Hart et al. 2016). In the present study, the mean values of duration of post-traumatic amnesia were 13.9 hours and 37.4 hours in group I and group II respectively with significant difference between the two groups. In the same line, Lange et al. (2012) reported significant difference between mild and moderate head injured patients regarding duration of post-traumatic amnesia.

Mean values of hospitalization period were 2.5 days in group I and 8.3 days in group II with a significant difference between the two groups (p-value < 0.001). Hospitalization period was found to be positively correlated to the severity of head injury. This is confirmed by findings of El-Sarnagawy et al. (2018) who reported shorter hospitalization period (less than 7 days) for mild cases compared to moderate cases who had a prolonged hospital stay for more than 7 days (p-value < 0.001).

Regarding the types of head injuries reported in the current study, scalp injuries were seen in 50% of patients where scalp contusions were the most frequently detected scalp injury followed by scalp cut wounds then contused wounds. This result is in partial agreement with the work of Wang et al. (2018) in China who documented scalp contusion as the most common scalp injury followed by contused wounds. High percentage of scalp injuries can be explained by loose areolar space and minimal musculature of the scalp (Pate et al. 2017).

In the current study 43.3% of patients had skull fractures. The reported type of fracture was fissure fracture. This result is in agreement with those reported by Aras et al. (2016) who found that 49% of their studied patients had fissure fractures. Moreover, vault fractures were more frequently reported than base fractures in the current study. A finding that could be explained on the basis that skull vault is more exposed so that it is more vulnerable to fracture compared to skull base (Rupani et al. 2013).

In this study, it was observed that 60% of the patients had meningeal hemorrhage. Subarachnoid hemorrhage was the most frequently detected meningeal hemorrhage (30%). Similarly, Nyanzu et al. (2017) in China reported subarachnoid hemorrhage as the most frequently detected brain vascular injury. On the other hand, our finding is in contrast with the Egyptian study of Hasanin et al. (2016) who reported extradural hemorrhage in the majority of their studied head injured patients. Moreover, brain injuries were observed in 6.7% of the studied head injured cases. Sogut et al.
(2010) reported brain injuries in 16% of their studied patients.

In the present study 60% of patients had multiple head injuries and this could be explained on the basis of data obtained where road traffic accidents and falls were responsible for most of head injuries. Road traffic accidents and falls are usually associated with multiple injuries (Refaat et al. 2019).

The study herein revealed that concentration of UCH-L1 in each of mild and moderate head injured patients was significantly higher in comparison with the control group. Moreover, UCH-L1 concentration in moderate head injured patients was significantly higher compared to mild head injured patients. Increased serum UCH-L1 concentration in cases of head injury could be explained by neuronal injury (Li et al. 2015). In line with these findings, Papa et al. (2012) reported significant elevation of serum UCH-L1 concentrations in mild and moderate traumatic head injured patients compared to the controls. Kou et al. (2013) reported that UCH-L1 concentration was elevated in mild head injured patients compared to control subjects. Singh et al. (2018) reported that moderately head injured patients exhibited significant higher UCH-L1 concentration compared to mild head injured patients. Conversely, Puvenna et al. (2014) studied patients with mild head injury and found no significant difference between patients and controls regarding UCH-L1 concentration.

There were no reported cases of death among the studied patients. Patients included in the current study were of mild and moderate severity only and severe cases were not included. According to Naveed (2010), most of mild and moderate head injured patients were managed conservatively with rare mortality.

Complications reported in the present head injured patients were post-traumatic neurosis, personality changes, cranial nerve injury, and infection. The psychiatric complications following THI were closely related to the acute changes in the neurotransmitters by altering levels of acetylcholine, dopamine, norepinephrine, and serotonin. Damage to the ascending monoaminergic projections leads to decrease in dopamine levels. Moreover, contusions of frontal cortex may interrupt serotonin pathways (Ahmed et al. 2017). Changes in cholinergic cortical transmission and norepinephrine level after THI are evident (Osier and Dixon 2016). The increased susceptibility of cranial nerve injuries following THI could be attributed to the fact that many cranial nerves run over surface of the skull. So that, cranial nerves may be injured due to direct trauma, tissue reaction at the fracture site, increased intracranial tension or associated infection (Patel et al. 2005). In addition, head injured patients are susceptible to infection. This could be explained by transient immune-depression triggered by brain damage. After trauma, there is a paralysis of monocyte function; suppression of T cell functions, and B-cell dysfunction (reduced capacity to produce antibodies) (Dziedzic et al. 2004; Kourbeti et al. 2012).

Statistical analysis of the current study revealed that the occurrence of complications was significantly higher in group II than group I. This was in accordance with Naalt (2001). Additionally, Lange et al. (2012) reported that personality changes were significantly higher in moderate head injured patients compared to mild head injured patients. In contrast, Misuc-pavkov et al. (2012) demonstrated that post-traumatic neurosis and personality changes were inversely proportional to the severity of head injury. However, these different results may be explained according
Dikmen et al. (2010) who stated that psychiatric and cognitive disorders after THI were related to age, sex, pre-injury alcohol / drug abuse, and pre-injury psychiatric history.

In the current study, there was no significant correlation between UCH-L1 concentration and age in all studied subjects. This result is in line with Kou et al. (2013) who reported that serum UCH-L1 concentrations did not correlate with age at the time of hospital admission.

In this study, there was no significant correlation between UCH-L1 concentration and pre-hospitalization period in all studied head injured patients whereas significant negative correlation between UCH-L1 concentration and pre-hospitalization period was observed in group I. This means that UCH-L1 is inversely correlated to the delay time in mild head injured cases. According to Puvenna et al. (2014), the kinetics of UCH-L1 is not well understood and UCH-L1 may show rapid decline in mild cases.

In head injury, the primary neuronal injury is followed by post-traumatic disruption of blood brain barrier. UCH-L1 is a small neuronal protein with a molecular weight of 24 KDa without known active transport mechanism. These features facilitate its crossing of blood brain barrier and stability in the biological fluids. This could justify positive correlation between UCH-L1 and severity of head injury as well as poor outcome (Liu et al. 2010; Yue et al. 2020). In the same line, significant positive correlation between UCH-L1 concentration and severity of head injury was observed in the current study. This is in agreement with the work of Mondello et al. (2012). In contrast, Siahaan et al. (2018) reported no correlation between UCH-L1 and head injury severity. This difference may be due to variation in the sample size, pre-hospital period, and time of sample collection. Moreover, there was a significant correlation between hospitalization period and UCH-L1 concentration in head injured patients. This result is in accordance with Singh et al. (2018) who found that the duration of hospital stay increased with increased UCH-L1 concentration. Moreover, significant positive correlation between UCH-L1 concentration and duration of post-traumatic amnesia was observed in the current study.

In the current study, patients presented with multiple head injuries were equally distributed among group I and group II (9 patients in each group). This could justify lack of significant correlation between UCH-L1 and number of injuries. On the other hand, the median concentration of UCH-L1 in the presence of complications (11.90 ng/ml) was significantly higher than in the absence of complications (0.04 ng/ml). This result is similar to the work of Papa et al. (2010) who reported that mean value of UCH-L1 in patients with complications after head injury was 43.1 ng/ml versus 6.1 ng/ml in those without complications ($p$-value = 0.002).

An interesting finding obtained from multiple regression analysis in the current study is that age and sex did not affect serum UCH-L1 concentration giving an important advantage to UCH-L1 as a forensic marker for cases with THI. Moreover, it was found that decrease in GCS by one unit was associated with a significant increase in UCH-L1 concentration by 4.077 units. Mondello et al. (2016) reported negative correlation between UCH-L1 concentration and GCS on admission. In addition, analysis of ROC curve showed that victims with UCH-L1 level above 0.2 ng/ml had a greater risk for complications. Up to the best of the authors' knowledge, no other studies identified a cut
Conclusions and Recommendations

In conclusion, UCH-L1 could be introduced as an optimistic biomarker in cases of THI in both forensic and clinical settings. The present study revealed that UCH-L1 had significant correlation with head injury severity and provided UCH-L1 as a tool that could predict complications at cutoff 0.2 ng/ml. It could be recommended to include UCHL1 in the routine investigations requested for patients of mild and moderate head injuries on admission.

Further studies are recommended on larger number of patients for more evaluation of the medico-legal application of UCHL1 in cases with head injury.

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الملخص العربي

التطبيق الطبي الشرعي لليوبكتين كربوكسي هيدرولاز الطرفى ل في مرضى إصابات الرأس الخفيفة والمتوسطة

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المقدمة: تعتبر إصابة الرأس سببًا شائعًا للوفاة والعجز في مصر وفي جميع أنحاء العالم. وكذلك فإن تقييم مريض إصابة الرأس مطلوب في المواقف المختلفة للطب الشرعي. وقد تم حديثاً إدخال المؤشرات الحيوية للتنبؤ بنتائج إصابات الرأس. واليوبكتين كربوكسي هيدرولاز الطرفى ل 1 هو أحد المؤشرات الحيوية الجديدة ذات المكونات العصبية المحددة.
وبدلاً من ذلك فإن الهدف من الدائرة الحالية هو تقييم التطبيق الطبي الشرعي لليوبكتين كربوكسي هيدرولاز الطرفى ل 1 لتنبؤ ب_TRUNCATED

نتاجحات: وقد أظهرت النتائج أن تركيز اليوبكتين كربوكسي هيدرولاز الطرفى ل 1 كان أعلى بدلالة إحصائية في المجموعة الأولى والثانية بالمقارنة مع المجموعة الثالثة وكذلك فقد كان تركيزه في المجموعة الثانية أعلى بدلالة إحصائية مقارنة بالمجموعة الأولى. كما لوحظ وجود ارتباط ذي دلالة إحصائية بين تركيز اليوبكتين كربوكسي هيدرولاز الطرفى ل 1 وكل من مدة الإقامة بالمستشفى ومدة فقدان الذاكرة الناتجة عن إصابة الرأس في كل المرضى. وكان متوسط تركيز اليوبكتين كربوكسي هيدرولاز الطرفى ل 1 في المرضى الذين أظهروا مضاعفات (11.9 نانوجرام / مل) أعلى بدلالة إحصائية من المرضى الذين لم يصابوا بمصاعفات (0.04 نانوجرام / مل). وقد أمكن لليوبكتين كربوكسي هيدرولاز الطرفى ل 1 أن يتنبأ حدوث مضاعفات إصابة الرأس عند قيمة القطع أكثر من 0.2 نانوجرام / مل.

الخلاصة: وقد خلصت هذه الدراسة إلى أن مستوى اليوبكتين كربوكسي هيدرولاز الطرفى ل 1 في الدم قد يكون مفيدًا لخبار الطبيب الشرعي لاتصال علامة سببية بين النتائج السلبية والإصابة في مرضى إصابات الرأس.

الكلمات المفتاحية: إصابة الرأس، اليوبكتين كربوكسي هيدرولاز الطرفى ل 1، مدى تطور، النتيج، مؤشرات.