Serum cleaved tau protein and traumatic mild head injury: a preliminary study in the Thai population

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Original Article

Abstract

Purpose To determine the correlation between serum cleaved tau protein and traumatic mild head injury (MHI) (GCS 13–15).

Methods A prospective observational study was conducted. Blood specimens from 12 healthy persons and 44 adult patients with traumatic MHI were collected in the emergency department to measure the cleaved tau protein level using a Human Tau phosphoSerine 396 ELISA kit. A brain computed tomography (CT) scan was done in all patients. The serum cleaved tau protein level was considered positive at a cut-off point of 0.1 pg/ml. An intracranial lesion was defined as any abnormality detected by brain CT scan.

Results The mean age of the traumatic MHI patients was 34.9 ± 15.6 years (range 15–74). The median GCS was 15. The median time from injury to arrival at the emergency department was 30 min. There were 11 intracranial lesions detected by brain CT scan (25.0 %). Serum cleaved tau protein was not detected in either healthy or traumatic MHI patients.

Conclusion As it was uncorrelated with traumatic MHI, serum cleaved tau protein proved to be an unreliable biomarker to use in the early detection of and decision-making for traumatic MHI patients at the emergency department.

Keywords Serum cleaved tau protein · Traumatic mild head injury · Emergency department · Biomarker

Introduction

Traumatic head injury is one of most common conditions of patients who visit the emergency department, and is associated with high morbidity and mortality among all traumatic patients [1, 2]. Currently, the diagnosis of head injury is based on history, mechanism of injury, Glasgow Coma Scale (GCS) score, and brain computed tomography (CT) scan. The patients are divided into three groups based on the GCS score: mild (GCS 13–15), moderate (GCS 9–12), and severe (GCS 3–8). For moderate and severe head injury patients, the indications to perform brain CT scan are clearly identifiable due to the high rate of positive intracranial lesions and the need for surgical intervention [3]. In traumatic mild head injury patients, there are some indications that a high-sensitivity brain CT scan should be performed: headache, vomiting, age >60 years old, intoxicated, short-term memory deficit, trauma above clavicle, seizure, failure to reach GCS 15 within 2 h after injury, and evidence of a fractured skull or base of skull fracture [4–7]. However, all of these diagnostic tools are indirect measurements that do not represent nerve cell pathology, and a brain CT scan cannot be performed in cases of hemodynamic instability. Also, there have been some patients with normal brain CT scans who developed post-concussion syndrome after closed head injury [8].

Several biomarkers have been developed to directly determine the pathology of the nerve cells in the central nervous system (CNS) when it is injured: neuron-specific enolase (NSE), S-100 B, and cleaved tau protein. NSE and S-100 B are not widely used due to their lack...
of specificity to the CNS [2, 9–12]. Cleaved tau proteins are microtubule-associated structural proteins found in the axons of the CNS that are released into the cerebrospinal fluid (CSF) and pass through the blood–brain barrier into the bloodstream when the nerves are injured, and serum cleaved tau proteins can be detected by ELISA using the specific antibody [13–16]. Measurements of cleaved tau protein in the CSF of head injury patients were higher than those for healthy persons, and were also higher than in patients with Alzheimer’s disease and normal pressure hydrocephalus [13, 14, 16]. Cleaved tau protein is a reliable and severity-dependent biomarker. Previous studies have indicated that a high CSF cleaved tau protein level is correlated with a high rate of poor prognosis [1, 16] and reflects brain injury [15, 17, 18]. Increased serum cleaved tau protein was associated with a greater chance of intracranial injury and poor outcome in patients with closed head injuries [1].

Songklanagarind Hospital receives about 10,000 traumatic patients annually, and 30–40 % of them have primary or associated head injury. The decision to perform brain CT scan in a case of traumatic mild head injury is based on the history and clinical examination. The use of a biomarker along with the history and a clinical examination may help to identify patients who need a brain CT scan, and may decrease the number of negative brain CT scan results, along with unnecessary radiation exposure. The objective is to determine the correlation between serum cleaved tau protein and traumatic mild head injury (GCS 13–15).

**Methods**

This was a prospective observational study conducted in a level I trauma center, university-based hospital from March 2010 to August 2010. The blood samples from 12 healthy volunteers (control group) and 44 traumatic mild head injury patients who visited the emergency department at Songklanagarind Hospital were collected after patients or their families signed informed consent. The demographic data, including time of injury and time of emergency room arrival, physiologic parameters, physical examination including GCS, and brain CT scan results, were prospectively recorded. The ethics committee board of the study institution approved this study.

**Patient eligibility**

The inclusion criteria were patients who were at least 15 years old with a clinical diagnosis of traumatic mild head injury (GCS 13–15). All of the patients had a brain CT scan performed. We excluded all patients referred from regional or provincial hospitals.

**Outcome assessment**

The blood samples were taken at the emergency department, and measurements for cleaved tau protein were performed using the Human Tau phosphoSerine 396 ELISA (hTau pS396) kit (BioSource International, Inc., Camarillo, CA, USA). The serum cleaved tau protein level was considered positive at a cut-off point of 0.1 pg/ml. All patients underwent brain CT scan (16-channel multidetector CT scanner, Brillance, Philips Medical Systems N.V., Amsterdam, Netherlands) using the conventional mode from the vertex of the skull to level 2 of the cervical spine, 5 mm in thickness, without intravenous contrast media administration. An intracranial lesion was defined as any trauma-associated intracranial abnormality detected by brain CT scan.

**Data analysis**

The results were reported as the number, mean, standard deviation (SD), median, and percentage (%). The level of serum cleaved tau protein was then compared between the control group and the traumatic mild head injury group using Student’s t test. Statistical significance was assumed for \( p < 0.05 \). The correlation of serum cleaved tau protein with traumatic mild head injury was evaluated based on the results from the clinical examination and brain CT scan. The sensitivity and specificity were calculated. A statistical analysis was not performed because the study did not detect any serum cleaved tau protein.

**Results**

The mean age of the traumatic mild head injury patients (35 males and 9 females) was 34.9 ± 15.6 years (range 19–74). The most common cause of the trauma was motorcycle accident (72.7 %). The median GCS was 15. The median time from injury to time of arrival at the emergency department was 30 min. Nineteen patients tested positive for alcohol consumption (Table 1). Serum cleaved tau protein could not be detected in either healthy persons or those with traumatic mild head injury. The brain CT scan results were negative in 33 patients, and 11 patients were positive for intracranial lesion: three cases of epidural hemorrhage, five cases of subdural hemorrhage, and three cases of subarachnoid hemorrhage. Six patients underwent surgical intervention (Table 2).
Discussion

Serum cleaved tau protein was not detected in either the healthy control group or the traumatic mild head injury patients. This may have been due to the early blood sample collection, as only 13 patients arrived at the emergency department 1 h or more after the time of injury; at this early stage after the injury, the level of serum cleaved tau protein in the blood circulation following passage across the blood–brain barrier would have been so low as to be undetectable. Blood storage over the weekend (2–3 days) before the test may also have affected the results.

We could not identify a correlation between the serum cleaved tau protein of patients with traumatic mild head injury and the results from the brain CT scans in this study. This result is similar to that reported by Ost and colleagues [19], who studied severe traumatic brain injury patients and noted that the total tau in the ventricular CSF probably reflects axonal damage, but were unable to detect serum cleaved tau protein. Bulut [20] found no significant difference in serum cleaved tau protein levels between the control group and mild head injury patients. Kavalci [21] also mentioned the limited value of using serum cleaved tau protein in the diagnosis of traumatic mild head injury. Guzel [22] reported that the serum cleaved tau protein level increased after traumatic mild head injury, but that it was not possible to use this increase in serum level to discriminate between patients with cranial lesions and those without cranial lesions, as demonstrated by brain CT scans.

In contrast, Liliang [23] studied biomarkers in traumatic severe head injury patients and found that, in addition to the GCS score, the serum cleaved tau protein level may serve as an indicator of outcome following traumatic severe head injury. The proportion of patients found by brain CT scan to be positive for intracranial lesions (25 %) in this study, none of whom had a detectable level of serum cleaved tau protein, was nearly twice as high as that seen in the study of Ma [24]. Furthermore, some researchers have reported a nonsignificant correlation between serum cleaved tau protein and post-concussion syndrome after traumatic mild head injury [25, 26]. Therefore, further investigation of the possibility of correlations of serum cleaved tau protein with intracranial lesions and post-concussion syndrome in the Thai population is needed.

Conclusion

Given that no correlation of serum cleaved tau protein level with traumatic mild head injury was observed, serum cleaved tau protein proved to be an unreliable marker to use in the early detection of and decision-making for traumatic mild head injury patients at the emergency department.

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**Conflict of interest** The authors declare that they have no conflict of interest.

**References**


