Published in final edited form as:

Am J Emerg Med. 2008 September ; 26(7): 763–768. doi:10.1016/j.ajem.2007.10.029.

Serum cleaved-tau does not predict postconcussion syndrome after mild traumatic brain injury

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Abstract

Objectives—Our objective was to determine if the biomarker for axonal injury, serum cleaved-tau (C-tau), predicts PCS in adults after mild traumatic brain injury (mTBI).

Methods—C-tau was measured from blood obtained in the emergency department. Outcome was assessed at three months post-injury using the Rivermead Postconcussion Symptoms Questionnaire (RPQ) and Acute Medical Outcomes SF-36v2™ Health Survey (SF-36).

Results—Out of 50 patients, there were 15 patients with detectable levels of C-tau, 10 patients with abnormal findings on initial head CT and 22 patients with PCS. One-third of patients with detectable C-tau and 14.3% of patients without detectable C-tau had abnormal findings on head CT ($p=0.143$). Serum C-tau was not detected more frequently in patients with PCS than those without, neither for all patients ($p=0.115$) nor the subgroup with negative head CT scans ($p=0.253$).

Conclusions—C-tau is a poor predictor of PCS after mTBI regardless of head CT scan result.

Keywords

brain injuries; post-concussion syndrome; biological markers; tau proteins

INTRODUCTION

Annually, over 1.2 million cases of mild traumatic brain injury (mTBI) are evaluated in US emergency departments [1]. The prevalence of post-concussion syndrome (PCS) at three months post-injury ranges from 24 to 84% [2]. Symptoms of PCS may be physical (headache and dizziness), cognitive (memory deficit and diminished concentration), or affective (anxiety and depression). Physicians currently have no readily available or reliable method for identifying those mTBI patients who will develop PCS. Early identification and treatment of PCS may be beneficial [3].

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Several central nervous system (CNS) biomarkers have been studied as potential tools to predict PCS after mTBI with equivocal success. The most widely studied biomarker to date has been S100B, which is localized to astroglial cells. Some studies have detected a relationship between serum levels of S100B and patient outcome [4,5], whereas others have not [1,6,7]. There are two published studies on acute serum levels of tau, a microtubule-associated structural protein localized to axons, after mTBI. There was no statistical difference between serum tau levels in mTBI patients compared to controls [8]. Serum tau levels after mTBI did not correlate with intracranial abnormalities on head computed tomography (CT) scans [8,9].

Cleaved-tau (C-tau) may represent a new biomarker for predicting PCS. Tau is proteolytically modified after axonal injury, and this cleavage product is known as C-tau. Serum C-tau levels may reflect CNS injury better than total tau levels. As axonal damage is also thought to underlie the neurologic dysfunction seen after mTBI, C-tau may have theoretical advantages over other CNS biomarkers. A previous report has shown that serum C-tau levels were predictive of intracranial injury and outcome after moderate and severe TBI [10]. One small study of 35 mTBI patients did not find an association between serum C-tau levels and severity of 3-month PCS symptoms [1]. Our study extends their findings by considering two other clinically important outcomes, radiographically apparent intracranial injury and global health status. In addition to causing PCS symptoms, mild TBI is known to adversely affect multiple health domains [11].

The objective of this preliminary study was to test our hypothesis that post-mTBI serum C-tau levels are elevated in those with radiographically apparent intracranial abnormalities, PCS, and worse health-related quality-of-life. If C-tau demonstrates acceptable sensitivity and specificity for intracranial injury, this assay may allow physicians to be more selective with use of intracranial imaging after mTBI. In addition, if serum C-tau can reliably predict PCS, early identification and treatment of patients at high risk for PCS may reduce morbidity.

METHODS

Study Design

We performed a prospective observational study of adults presenting to an urban Level I trauma center after mTBI. The study was approved by the Institutional Review Board.

Study Setting and Population

The study was conducted at an urban tertiary care hospital with an annual census of about 85,000 visits. The hospital is an American College of Surgeons Level 1 trauma center.

A convenience sample of patients was enrolled between October 2003 and May 2004. Patients aged eighteen years or older were included if they had recent mTBI, defined as loss of consciousness (LOC) and/or post traumatic amnesia (PTA), and presented to the study hospital within 12 hours of trauma with a Glasgow Coma Scale (GCS) between 13–15. Intracranial imaging was not required for patient inclusion.

Patients were excluded if they had focal neurologic deficits, a penetrating injury to the skull, history of CNS surgery, CNS infection, transient ischemic attack, ischemic stroke, or intracranial hemorrhage in the past 30 days, or history of Alzheimer's disease, Parkinson's disease, seizure disorder, multiple sclerosis, bipolar, depression or schizophrenia. In addition, patients with an initial serum ethanol level equal to or greater than 100 mg/dL were excluded; high serum ethanol levels may impair the clinical assessment of mTBI impairments.

Study Protocol

Patient eligibility was determined by trained research assistants in consultation with the treating physician. All patients or their families (in cases where patients were impaired) gave informed consent prior to study inclusion. Demographic data and details of the traumatic event were collected on a standardized case report form at the time of ED presentation by research assistants. Data missing from the case report form were obtained by searching the medical records. In two cases where it appeared that emergency medical services (EMS) were promptly notified after the accident, the earliest time recorded on the EMS run sheet (dispatch or arrival time) was used as a surrogate for a missing time of injury. After three months, subjects were contacted by telephone by investigators blinded to both CT scan results and serum C-tau levels. Responses to the Rivermead Postconcussion Symptoms Questionnaire (RPQ) and Acute Medical Outcomes SF-36v2™ Health Survey (SF-36) were recorded. The order of the questionnaires was randomized. All data were entered into a customized Microsoft Access database (Microsoft Corporation, Redmond, WA).

C-tau Assay

Venous blood was obtained from patients during their emergency department (ED) stay. Blood was drawn into serum separator tubes and centrifuged at 13,000 g for 15 minutes. The resulting serum was stored frozen until ready for use. The C-tau enzyme-linked immunosorbent assay (ELISA) uses three monoclonal antibodies that recognize C-tau [1]. The lowest detection limit of our serum C-tau ELISA is 1.5 ng/ml (which was considered “0” in all analyses). The detailed pharmacokinetics of C-tau is not known, therefore, only the presence or absence of C-tau was used to address our study hypothesis.

Outcome Measures

The outcome measures were (1) initial head CT, (2) RPQ, and (3) SF-36. The final attending radiologist interpretation of the initial head CT scan was used. Skull fracture was not considered an intracranial abnormality. If traumatic intracranial abnormalities were not definitively excluded on initial head CT scan, subsequent imaging was typically performed. The principal investigator determined whether the initial CT scan was positive or negative for traumatic abnormality based on subsequent imaging and hospital course for the two subjects that had an equivocal initial head CT scan.

The RPQ asks patients to compare current severity of sixteen symptoms of PCS with premorbid severity, using values from 0 to 4, with higher scores representing worse symptoms. Total PCS scores were taken as the sum of all symptom scores excluding ratings of 1 because these indicate that the symptoms were unchanged from prior to injury. This provides a numerical score for PCS severity [12]. In addition, patients were classified as having PCS if they scored a two or higher on at least three questions. The questionnaire has high test-retest and inter-rater reliability [12].

The SF-36 measures self-perceived physical and mental health status across multiple domains. The SF-36 has demonstrated promise as a sensitive and valid measure of mTBI-related effects [11,13]. A cognitive function scale has been demonstrated to improve the sensitivity of the SF-36 for measuring cognitive outcomes after TBI, and those four additional questions were added to the administered SF-36 [14]. Higher scores indicate better functioning.

Data Analysis

Data have been summarized using frequencies and percentages for categorical data and means and standard deviations for continuous variables. Confidence intervals for proportions have been computed using the score method with continuity correction. Student’s t-test has been

used to compare continuous variables, and Fisher's Exact test has been used to compare categorical variables between groups. Data were analyzed using SPSS v 14.0 (SPSS Inc, Chicago, IL) and Microsoft Excel (Microsoft Corporation, Redmond, WA). Subgroup analysis of patients with a negative initial head CT scan was planned before data collection.

RESULTS

Fifty patients were enrolled. Age, race, gender, and mechanism of injury are described in Table 1, stratified by whether or not serum C-tau was detected. There were 15 patients with detectable levels of C-tau (30.0%, 95CI 18.3% to 44.8%). Of these 15 patients, the mean serum C-tau concentration was 5.02 ng/ml (SD 2.98 ng/ml). The time from injury to measurement of C-tau was similar between groups (Table 1).

Fourteen percent of patients with a GCS of 15 and 35.7% of patients with a GCS of 13 or 14 had at least one traumatic abnormality on head CT (described in Table 2). Abnormal findings on CT were similarly likely among those with and without C-tau. The sensitivity and specificity for intracranial abnormality on head CT were 50.0% (95CI 20.1–79.9%) and 75.0% (95CI 58.5–86.8%), respectively.

The mean time to follow-up was 20 weeks (SD 6 weeks). There was no difference in time to follow-up between those with and those without a measurable C-tau level ($p=0.223$). Due to cognitive impairments, one patient had his wife answer questions on his behalf. Two patients could not be contacted by telephone and completed the questionnaires after they were mailed to them. Nine patients were lost to follow-up. Of the subjects who underwent follow-up, the proportion with PCS was similar between those with and without C-tau detected. The sensitivity and specificity for PCS were 22.7% (95CI 8.7 – 45.8%) and 52.6% (95CI 29.5 – 74.8%), respectively. Even though only the presence or absence of C-tau in serum was used to address our study hypothesis, we decided to determine if there might be an underlying association between absolute serum C-tau levels, timing of blood draw, and outcome. There does not appear to be an association between serum C-tau levels, timing of blood draw, head CT results, and PCS (Figure 1).

Among all patients, the RPQ score was lower (fewer or less severe symptoms) among those with measurable C-tau than among those without measurable C-tau. The SF-36 mental component summary score was higher, which represents better functioning, among those with detectable C-tau than among those without detectable C-tau. The two groups did not differ on the SF-36 physical component summary score or cognitive component summary score.

Subgroup analysis of all patients with a negative initial head CT scan was performed. Among the 31 patients with a negative head CT scan and who were followed up, C-tau was detected in 9. Four out of the nine (44.4%) with detectable C-tau had PCS, while 15/22 (68.2%) without detectable C-tau had PCS ($p=0.253$). In this subgroup, the sensitivity and specificity for PCS were 21.1% (95CI 7.0 – 46.1%) and 58.3% (95CI 28.6 – 83.5%), respectively. Those with detectable C-tau scored better on the RPQ (5.7 v 16.4, $p=0.011$) and the SF-36 mental component (57.6 v 44.5, $p=0.005$), than those who did not. Subjects with detectable C-tau did not differ from those without detectable C-tau on the SF-36 physical component summary score (46.3 v 48.8, $p=0.379$) or cognitive component summary score (72.7 v 62.9, $p=0.182$).

DISCUSSION

Despite an absolute difference of 19% between head CT abnormalities in patients with and without detectable C-tau, this result was not statistically significant. A larger sample size may better elucidate an association, if any. As tau is localized to axons, serum C-tau levels may correlate better with axonal injury, which is not readily detectable by CT scanning. In our study,

axonal injury was detected by CT in one patient, who had a serum C-tau level of 4.98 ng/ml. White matter injury revealed by magnetic resonance imaging (MRI) may better correlate with C-tau levels.

The presence of C-tau in serum within 12 hours of injury did not predict PCS at follow-up regardless of head CT results. A positive association between PCS and C-tau was also not demonstrated in one other small study [1]. Using the same cut-off between normal and abnormal serum levels as we did, their sensitivity and specificity of C-tau for PCS were 43.8% (95CI 23 – 67%) and 71.4% (95CI 45 – 88%), respectively. Our two studies captured seemingly different but complementary mTBI populations. Our cohort appeared to be more severely injured as we enrolled patients with a higher rate of CT-detectable abnormalities (20% versus 7%) and lower GCS scores (28% versus 6% of total patients had initial GCS of 13 or 14). Taken together, our studies strongly suggest that detectable C-tau in serum does not predict PCS in the entire spectrum of mTBI patients.

In our study, patients with detectable serum C-tau unexpectedly scored better on the RPQ and the mental component of the SF-36. Tau is localized to axons and is proteolytically modified after axonal injury. Injury isolated to gray matter is not expected to cause an acute release of C-tau into the CSF or serum. Patients with detectable serum C-tau may have suffered predominantly white matter injury, and this cohort may have a better prognosis than patients with predominantly gray matter injury.

Three potential limitations of this study are small sample size, the use of head CT to diagnose intracranial injury, and reliance on self-report measures (RPQ and SF-36). First, our small sample resulted in low statistical power to detect an association, if any, between serum C-tau, PCS, and CT-detectable intracranial abnormalities. The negative findings observed here might have been due to the small sample sizes. A post hoc power analysis suggested we would have had 80% power to detect a difference in proportions between those with and without detectable C-tau of about 38%. Smaller effects would not have been found to be statistically significant. Second, MRI is more sensitive than CT for detecting white matter lesions, which may be more likely than other types of intracranial injury to acutely elevate serum levels of C-tau; MRI-detectable intracranial abnormalities may more strongly correlate with elevated serum C-tau levels. Third, as post-mTBI symptoms are believed to arise out of the interactions between premorbid, injury-related, and post-morbid neuropathological and psychological factors [15], the self-reporting of symptoms may have limitations as a measure of mTBI effects. Symptoms of PCS do not necessarily correlate with neurocognitive test performance after mTBI [16]; neurocognitive testing may better quantify mTBI-related impairments while minimizing the confounding effects of other factors.

In conclusion, there is some indication that elevated serum C-tau may be associated with CT-detectable intracranial abnormalities but the assay is unlikely to be useful as a clinical risk stratification tool to determine need for intracranial imaging after mTBI. In addition, this assay does not appear to be useful in identifying patients at high risk for PCS after mTBI regardless of head CT scan results.

ACKNOWLEDGEMENT PAGE

The authors thank Dr. Robert Neumar, MD, PhD for his insight in editing the manuscript.

Research supported by National Institutes of Health grant R43-NS46822 (FPZ).

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Figure 1.

Plots demonstrating serum C-tau levels versus blood draw time stratified by the presence or absence of 3-month PCS in all patients (A). Patients were further subdivided by head CT results (B and C). One patient with a serum C-tau level of 3.41 ng/ml was not included in the plots. Time of blood draw from injury was estimated to be between 4.5 and 8 hours. This patient had abnormal findings on head CT, and was found not to have PCS.

Table 1

Characteristics of patients in the study, stratified by whether or not serum C-tau was detected. Data are frequencies and percents or means and standard deviations as appropriate.

	All (N=50)	C-tau detected No (N=35)	Yes (N=15)	p-value ^a
Age	40.3	37.3	47.5	0.062
Race				
Caucasian	38	24	14	(93.3)
African American	9	9	0	(0.0)
Other	2	2	0	(0.0)
Unknown	1	0	1	(6.7)
Sex				
Male	38	25	13	(86.7)
Female	12	10	2	(13.3)
Mechanism of injury ^b				
Fall from standing height	5	4	1	(6.7)
Fall from greater than standing height	9	5	4	(26.7)
Assault	1	0	1	(6.7)
Pedestrian struck	3	2	1	(6.7)
MVC	30	22	8	(53.3)
Glasgow Coma Score				
13	3	3	0	(0.0)
14	11	6	5	(33.3)
15	36	26	10	(66.7)
Abnormal head CT	10	5	5	(33.3)
Time to measurement of C-tau (in hours) ^c	5.0	4.8	5.4	0.502
Followed up after 3 months	41	27	14	(93.3)
RPQ ^d				
Classified as having PCS (N=41)	22	17	5	(35.7)
Total score (N=41)	12.6	16.6	4.9	(5.8)
SF-36 ^d				
Physical component score (N=37)	47.9	48.2	47.4	(4.6)
Mental component score (N=37)	48.5	44.9	55.1	(9.1)
Cognitive summary score (N=41)	67.2	63.9	73.5	(10.4)

^a p-values reported for differences between patients with and without detectable C-tau.

^b data missing for two patients.

^c data missing for one patient; time of injury could only be estimated to within a 3.5 hour window.

^d 27 and 24 patients without detectable C-tau completed the RPQ (plus cognitive scale) and SF-36, respectively. 14 and 13 patients with detectable C-tau completed the RPQ (plus cognitive scale) and SF-36, respectively.

Table 2

Prevalence of CT-demonstrated intracranial abnormalities

Type of intracranial abnormality	Number ^a
Intraparenchymal hemorrhage	7
Subarachnoid hemorrhage	6
Subdural or epidural hematoma	2
Other ^b	3

^aPatients may have more than one type of intracranial abnormality on head CT scan.

^bOne patient each with hemorrhagic shear injury, intraventricular hemorrhage, and pneumocephalus.