Glial fibrillary acidic protein in traumatic brain injury

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Glial fibrillary acidic protein (GFAP) is a significant biomarker in the context of traumatic brain injury (TBI). GFAP is a type of intermediate filament protein found predominantly in astrocytes, which are star-shaped glial cells in the central nervous system (CNS). When brain injury occurs, astrocyte becomes damaged or stressed, leading to the release of GFAP into the bloodstream. This makes GFAP a useful biomarker for detecting brain injury, particularly TBI.

Key points

1. **Early Detection**: GFAP levels rise rapidly after a TBI, making it a valuable marker for early detection of brain injury. Elevated GFAP levels can often be detected within hours of the injury, and sometimes even within minutes, as indicated in the study you referenced.

2. **Specificity for CNS Injury**: GFAP is relatively specific to the CNS, which means that its presence in the blood is a strong indicator of brain injury, as opposed to injuries in other parts of the body. This specificity helps in differentiating TBI from other types of trauma.

3. **Predicting Severity**: Higher levels of GFAP are often associated with more severe brain injuries. Studies have shown that GFAP levels correlate with the presence of intracranial lesions on CT scans, the need for neurosurgical intervention, and other adverse outcomes in TBI patients.

4. **Clinical Utility**: GFAP is being investigated for its potential use in clinical settings to guide the management of TBI patients. For example, it could help in triaging patients, deciding who needs further imaging like CT scans, and predicting long-term outcomes.

5. **Research and Development**: GFAP is part of ongoing research into biomarker panels that might one day be used in emergency and prehospital settings to quickly assess TBI severity, even before a

patient reaches the hospital.

In summary, GFAP is a promising biomarker for traumatic brain injury, offering the potential for early detection, severity assessment, and guiding clinical decision-making in TBI management.

Papa et al. examine the performance of glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), and microtubule-associated protein 2 (MAP-2) within 30 and 60 minutes of TBI in identifying intracranial lesions on computed tomography (CT) scan, need for neurosurgical intervention (NSI), and clinically important early outcomes (CIEO).

This cohort study is a biomarker analysis of a multicenter prehospital TBI cohort from the Prehospital Tranexamic Acid Use for TBI clinical trials conducted across 20 centers and 39 emergency medical systems in North America from May 2015 to March 2017. Prehospital hemodynamically stable adult patients with traumatic injury and suspected moderate to severe TBI were included. Blood samples were measured for GFAP, UCH-L1, and MAP-2. Data were analyzed from December 1, 2023, to March 15, 2024.

Main outcomes and measures: The presence of CT lesions, diffuse injury severity on CT, NSI within 24 hours of injury, and CIEO (composite outcome including early death, neurosurgery, or prolonged mechanical ventilation ≥7 days) within 7 days of injury.

Of 966 patients enrolled, 804 patients (mean [SD] age, 41 [19] years; 418 [74.2%] male) had blood samples, including 563 within 60 minutes and 375 within 30 minutes of injury. Among patients with blood drawn within 30 minutes of injury, 212 patients (56.5%) had CT lesions, 61 patients (16.3%) had NSI, and 112 patients (30.0%) had CIEO. Among those with blood drawn within 60 minutes, 316 patients (56.1%) had CT lesions, 95 patients (16.9%) had NSI, and 172 patients (30.6%) had CIEO. All biomarkers showed significant elevations with worsening diffuse injury on CT within 30 and 60 minutes of injury. Among blood samples taken within 30 minutes, GFAP had the highest area under the receiver operating characteristic curve (AUC) to detect CT lesions, at 0.88 (95% CI, 0.85-0.92), followed by MAP-2 (AUC, 0.78; 95% CI, 0.73-0.83) and UCH-L1 (AUC, 0.75; 95% CI, 0.70-0.80). Among blood samples taken within 60 minutes, AUCs for CT lesions were 0.89 (95% CI, 0.86-0.92) for GFAP, 0.76 (95% CI, 0.72-0.80) for MAP-2, and 0.73 (95% CI, 0.69-0.77) for UCH-L1. Among blood samples taken within 30 minutes, AUCs for NSI were 0.78 (95% CI, 0.72-0.84) for GFAP, 0.75 (95% CI, 0.68-0.81) for MAP-2, and 0.69 (95% CI, 0.63-0.75) for UCH-L1; and for CIEO, AUCs were 0.89 (95% CI, 0.85-0.93) for GFAP, 0.83 (95% CI, 0.78-0.87) for MAP-2, and 0.77 (95% CI, 0.72-0.82) for UCH-L1. Combining the biomarkers was no better than GFAP alone for all outcomes. At GFAP of 30 pg/mL within 30 minutes, sensitivity for CT lesions was 98.1% (95% CI, 94.9%-99.4%) and specificity was 34.4% (95% CI, 27.2%-42.2%). GFAP levels greater than 6200 pg/mL were associated with a high risk of NSI and CIEO.

In this cohort study of prehospital patients with TBI, GFAP, UCH-L1, and MAP-2 measured within 30 and 60 minutes of injury were significantly associated with traumatic intracranial lesions and diffuse injury severity on CT scan, 24-hour NSI, and 7-day CIEO. GFAP was the strongest independent marker associated with all outcomes. This study sets a precedent for the early utility of GFAP in the first 30 minutes from injury in future clinical and research endeavors [1)]

A study aimed to determine whether this context of use can be expanded beyond 12h post-TBI in patients presenting with Glasgow Coma Scale (GCS) 13-15. The prospective, 18-center Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study enrolled TBI participants aged ≥17 years who presented to a United States Level 1 trauma center and received a clinically indicated brain CT scan within 24h post-injury, a blood draw within 24h and at 14 days for biomarker analysis. Data from participants with emergency department arrival GCS 13-15 and biomarker values at days 1 and 14 were extracted for the primary analysis. A subgroup of hospitalized participants with serial biomarkers at days 1, 3, 5, and 14 were analyzed, including plasma GFAP and UCH-L1, and serum neuron-specific enolase (NSE), and S100 calcium-binding protein B (S100B). The primary analysis compared biomarker values dichotomized by head CT results (CT+/CT-). The area under the receiver-operating characteristic curve (AUC) was used to determine diagnostic accuracy. The overall cohort included 1142 participants with initial GCS 13-15, with a mean age of 39.8 years, 65% male, and 73% Caucasian. The GFAP provided good discrimination in the overall cohort at days 1 (AUC = 0.82) and 14 (AUC = 0.72), and in the hospitalized subgroup at days 1 (AUC = 0.84), 3 (AUC = 0.88), 5 (AUC = 0.82), and 14 (AUC = 0.74). The UCH-L1, NSE, and S100B did not perform well (AUC = 0.51-0.57 across time points). This study demonstrates the utility of GFAP to aid in decision-making for diagnostic brain CT imaging beyond the 12-hour time frame in patients with TBI who have a GCS 13-15 [2)]

The objective of the study was to determine whether two day-of-injury blood-based biomarkers are predictive of posttraumatic stress disorder (PTSD). We used data from 1143 individuals with mild TBI (mTBI; defined as admission Glasgow Coma Scale [GCS] score 13-15) enrolled in TRACK-TBI, a prospective longitudinal study of level 1 trauma center patients. Plasma glial fibrillary acidic protein (GFAP) and serum high sensitivity C-reactive protein (hsCRP) were measured from blood collected within 24 hours of injury. Two hundred and twenty-seven (19.9% of) patients had probable PTSD (PCL-5 score ≥ 33) at 6 months post-injury. GFAP levels were positively associated (Spearman's rho = 0.35, $p < 0.001$) with duration of posttraumatic amnesia (PTA). There was an inverse association between PTSD and (log)GFAP (adjusted OR = 0.85, 95% CI 0.77-0.95 per log unit increase) levels, but no significant association with (log)hsCRP (adjusted OR = 1.11, 95% CI 0.98-1.25 per log unit increase) levels. Elevated day-of-injury plasma GFAP, a biomarker of glial reactivity, is associated with a reduced risk of PTSD after mTBI. This finding merits replication and additional studies to determine a possible neurocognitive basis for this relationship [3)]

Richter et al. aimed to assess if day of injury serum protein biomarkers could identify critically ill TBI patients in whom the risks of transfer are compensated by the likelihood of detecting management-altering neuroimaging findings.

Data were obtained from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. Eligibility criteria included: TBI patients aged ≥ 16 years, Glasgow Coma Score (GCS) < 13 or patient intubated with unrecorded pre-intubation GCS, CT with Marshall score < 3, serum biomarkers (GFAP, NFL, NSE, S100B, Tau, UCH-L1) sampled ≤ 24 h of injury, MRI < 30 days of injury. The degree of axonal injury on MRI was graded using the Adams-Gentry classification. The association between serum concentrations of biomarkers and Adams-Gentry stage was assessed and the optimum threshold concentration identified, assuming different minimum sensitivities for the detection of brainstem injury (Adams-Gentry stage 3). A cost-benefit analysis for the USA and UK health care settings was also performed.

Among 65 included patients (30 moderate-severe, 35 unrecorded) axonal injury was detected in 54 (83%) and brainstem involvement in 33 (51%). In patients with moderate-severe TBI, brainstem injury was associated with higher concentrations of NSE, Tau, UCH-L1 and GFAP. If the clinician did not want to miss any brainstem injury, NSE could have avoided MRI transfers in up to 20% of patients. If a 94% sensitivity was accepted considering potential transfer-related complications, GFAP could have avoided 30% of transfers. There was no added net cost, with savings up to £99 (UK) or $612 (US). No associations between proteins and axonal injury were found in intubated patients without a recorded pre-intubation GCS.

Serum protein biomarkers show potential to safely reduce the number of transfers to MRI in critically ill patients with moderate-severe TBI at no added cost [4].

Traumatic brain injury (TBI) is frequently associated with abnormal blood-brain barrier function, resulting in the release of factors that can be used as molecular biomarkers of TBI, among them GFAP, UCH-L1, S100B, and NSE. Although many experimental studies have been conducted, clinical consolidation of these biomarkers is still needed to increase the predictive power and reduce the poor outcome of TBI. Interestingly, several of these TBI biomarkers are oxidatively modified to carbonyl groups, indicating that markers of oxidative stress could be of predictive value for the selection of therapeutic strategies [5].

Serum from 51 critically injured trauma patients was prospectively collected on admission and on hospital day 2. All patients underwent an admission head computed tomography (CT) scan as a part of their clinical evaluation. Patients with facial fractures in the absence of documented TBI and patients with spinal cord injury were excluded. Demographic and outcome data were collected prospectively. Serum GFAP was measured in duplicate using enzyme-linked immunosorbent assay techniques.

Results: Thirty-nine (76%) of the 51 patients had CT-documented TBI. The study cohort was 72.5% men with a mean age of 43 years and a mean Injury Severity Score (ISS) of 30.2. There were no statistically significant demographic differences between the two groups. At admission day, the mean GFAP level in non-TBI patients was 0.07 pg/mL compared with 6.77 pg/mL in TBI patients ($p = 0.002$). On day 2 the mean GFAP level was 0.02 in non-TBI patients compared with 2.17 in TBI patients ($p = 0.003$). Using regression analysis to control for age, sex, and ISS, the Head Abbreviated Injury Scale was predictive of the level of GFAP on both days 1 and 2 (p values 0.006 and 0.026, respectively). Although GFAP levels were not predictive of increased hospital length of stay, intensive care unit length of stay, or ventilator days, high GFAP levels on hospital day 2 were predictive of mortality when controlling for age, sex, and ISS (odds ratio 1.45, p-value 0.028). The area under the receiver operating characteristic curve for GFAP was 0.90 for day 1 and 0.88 for day 2. A GFAP cutoff point of 1 pg/mL yielded 100% specificity and 50% to 60% sensitivity for TBI.

Conclusions: GFAP is a serum marker of TBI, and persistent elevation on day 2 is predictive of increased mortality. Excellent specificity for CT-documented brain injury was found using a cutoff point of 1 pg/mL [6].

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