In search of cost-effective and non-invasive biomarkers of traumatic brain injury

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Traumatic brain injury (TBI) is a major cause of morbidity and mortality internationally, with an estimated 69 million individuals estimated to sustain a TBI annually.[1] There exists heterogeneity in both the initial presentation of TBI, spanning from concussion to severe TBI, as well as recovery following these injuries. There are also inconsistencies in clinical care practices for the evaluation and management of TBI. The initial diagnosis of TBI and prognosis afterward is an important area of study with a need for cost-effective and safe tools to guide decision-making. To help address these critical issues, Whitehouse and colleagues investigated the relationship between baseline computed tomography (CT) imaging findings and concentrations of six serum biomarkers (i.e., GFAP, NFL, NSE, S100B, t-tau, and UCH-L1) obtained within 24 hours following all severities of TBIs.[2]

Their findings demonstrated an association between baseline intracranial lesion burden and serum biomarker levels among 2,869 patients from the CENTER-TBI study (median age 49, 68% male, 95% White and European).[2] A majority of TBIs were mild (Glasgow Coma Scale of 13-15) and serum biomarker concentrations reflected injury severity based on CT imaging. Parenchymal injury was associated with the highest serum biomarker concentrations. They did not observe a relationship between the serum biomarkers measured and etiology of injury.

Previous research from the CENTER-TBI study showed the six serum biomarkers examined by Whitehouse *et al* were accurate predictors of clinical severity, treatment and diagnostic path, and the presence of CT abnormalities.[3] Serum markers of neuroinflammation, axonal injury, and/or neuronal loss, especially UCH-L1 and GFAP, have consistently been shown to accurately predict acute TBI severity and associated outcomes in other cohorts.[4–6] Serum biomarkers also have utility for the detection of mild TBI and subconcussive injuries.[7–9] The novelty of the findings from Whitehouse *et al* lies in the large prospective cohort and examination of the association between the serum biomarkers and lesion type and lesion burden on CT imaging. The results are noteworthy for their possible implications for the clinical management of TBI and the insight they provide into injury pathophysiology.

Acute serum biomarkers could provide valuable additional information for clinical decision making following TBI. For example, serum biomarkers could guide, augment, or potentially replace data obtained from CT imaging. Notably, Whitehouse *et al* report an elevation in the measured biomarkers following isolated skull fracture without underlying parenchymal injuries determined by CT. The authors suggest that such extracranial injury can cause insult to the brain that may not be clinically detected by CT imaging. CT is less able to detect clinically relevant diffuse axonal injury (DAI) than magnetic resonance imaging, so a subset of these cases may represent TBI inadequately identified based on CT. Although the authors did not find an association between the serum biomarkers and DAI, this is likely because CT imaging measured DAI as opposed to diffusion MRI. The addition of a serum biomarker panel could potentially improve the diagnosis of TBI in patients presenting with DAI, which might otherwise be difficult to capture using CT, and result in triage to more appropriate clinical management. Furthermore, by identifying those in need of more advanced clinical care, a serum biomarker panel could potentially help reduce healthcare disparities by reducing the need for advanced imaging studies in areas with limited access to these devices.

In the case of mild TBI, a biomarker panel could conceivably provide additional ease for clinicians to rule out intracranial injury. CT imaging is often

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unremarkable following mild TBI and results in hazardous radiation and high healthcare costs. It is in this context that the US Food and Drug Administration recently approved UCH-L1 and GFAP for the clinical necessity of obtaining a CT scan following TBI.[10] However, these results suggest that a panel of biomarkers, each with a different profile, could be utilized to increase specificity and further reduce unnecessary CT imaging.

Serum biomarkers can provide insight into pathophysiology of injury, especially as it relates to prognosis. In this study, the authors report no association between injury mechanism and measured biomarkers but did find a relationship between extent of intracerebral edema and serum biomarker levels of GFAP, NFL, NSE, t-tau, and UCH-L1. This finding suggests that the elevated biomarkers respond to tissue damage in ways that may be relevant to recovery. Given that each biomarker is associated with different cell types or structures, any relationship between specific biomarkers and clinical symptoms warrants further study and may present unique targets for future intervention.

These findings should be cautiously interpreted based on the unique cohort studied and changes to clinical practices based on them would be premature at this time. The cohort was predominantly white (95%) and had severe enough injury to present to the emergency department. To illustrate the uniqueness of this sample, of the 68% of those in this cohort that presented with mild TBI, 51% had acute abnormality on CT scan. As a result, this sample represents the more severe end of even the mild TBI spectrum, and these findings may not fully translate to other settings such as the sports sideline. The high rate of missing data and associated exclusions of participants might have contributed to sample selection bias.

The data presented by Whitehouse *et al* provide promising evidence for the efficacy of serum biomarkers in tracking acute TBI severity. Additional study is warranted to determine if and how well these biomarkers can predict outcome following injury, and to what extent these findings can be expanded to other settings, including frontline settings like the paramedic services, athletic sideline assessments, and military combat settings.

Declaration of interests

The authors declare no conflict of interest.

Contributors

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