EDITORIAL

Tau as a Biomarker of Concussion

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The search for blood biomarkers useful in the management of traumatic brain injury (TBI) has been one of the holy grails of the clinical neurosciences for several decades. Biomarkers are molecules that can be measured in accessible biological fluids that reflect physiological, pharmacological, or disease processes and can suggest the etiology of, susceptibility to, activity levels of, or progress of a disease. According to the US Food and Drug Administration, biomarkers fall into 3 categories, which are not mutually exclusive: prognostic, predictive, and pharmacodynamic.[1] Prognostic biomarkers are baseline measurements that categorize patients by degree of risk for disease progression and inform about the natural history of the disorder. Predictive biomarkers are baseline characteristics that categorize patients by their likelihood of response to a particular treatment. Finally, pharmacodynamic biomarkers are dynamic measurements that show that biological response has occurred in a patient after a therapeutic intervention. Biomarkers have historically been critical to progress in a broad range of clinical conditions. Diagnostic and therapeutic advances in fields as disparate as cardiology and oncology have relied on the ability to measure biomarkers that are reliable indicators of the underlying pathology.

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Clinicians evaluating and treating patients who have sustained TBIs in the mild end of the spectrum and present after a brief period of altered awareness and brief (or no) loss of consciousness are faced with several questions that could benefit from the availability of validated blood biomarkers. Does this patient need to be transported to a hospital (usually by ambulance and at significant expense) for further evaluation, or is observation in place adequate, either on the sidelines of a sporting event or at home? Does this patient need a neuroimaging study, which is usually a cranial computed tomographic scan that involves radiation and, in young children, use of sedation to prevent movement? Is this patient likely to make a complete recovery after his or her concussion, or is he or she at risk for persistent postconcussive symptoms (PCS) for weeks, months, or longer? While most patients fully recover from a mild TBI (mTBI, a term now considered synonymous with concussion), a significant minority do not, and the ability to predict early on whether there is high risk of persistent PCS would be very useful for counseling and for the development of preventive strategies. Finally, what about the patient who presents with months or years of cognitive, behavioral, or psychological problems after 1 or multiple TBIs? Are the symptoms primarily due to an organic brain disorder, or should evaluation and treatment be focused on psychological factors?

The study by Shahim et al[2] in *JAMA Neurology* represents an important contribution to this field and introduces an innovative technology that may have wide applicability. The investigators studied professional ice hockey players from 2 teams in the Swedish Hockey League. A total of 288 players were studied at baseline, 35 of whom had a concussion during a half season (September 2012 to January 2013). Twenty-eight of these were evaluated after the concussion, and blood was drawn at 1, 12, 36, 48, and 144 hours after injury. This represents a strong study design. The high prevalence of concussion in professional athletes allows the collection of blood prior to the index mTBI (although obviously not prior to concussions they sustained in prior seasons), which increases the confidence in the results. Also importantly, professional athletes are typically psychologically robust and have little or no conscious or unconscious incentive to overreport PCS. While only 3 of the 28 players had a period of unconsciousness, 15 had PCS persisting beyond the time of the last blood collection, indicating the nontrivial nature of these seemingly mild injuries.

The most novel feature of the study is the use of an innovative digital immunoassay technology, which allows measurement of total tau in plasma.[3,4] The digital immunoassay for tau is 3000-fold more sensitive than standard immunoassays, allowing the detection of proteins found in circulation in subfemtomolar concentrations. In addition to assaying plasma total tau, the investigators also studied 2 other biomarkers that have long been a focus of research in the TBI field, neuron-specific enolase (NSE), a product of neurons, and S-100 calcium-binding protein B (S-100B), a product of activated astrocytes.

The main finding of the study is that total tau is elevated in plasma after a concussion, and the elevation persists for several (up to 6) days. This is an important finding, as tau is a widely studied brain-specific molecule involved in a wide range of neurodegenerative conditions, including chronic traumatic encephalopathy.[5] Total tau may be useful as a prognostic biomarker, as there was a good correlation between total tau elevations 1 hour after concussion and the number of days it took for symptoms to resolve. Using receiver operating characteristic analysis, total tau at 1 hour had high diagnostic accuracy (area under the receiver operating characteristic curve = 0.80) for discriminating players who had a concussion from those who had played in a friendly game and were not concussed, and it had even better prognostic accuracy for identifying players who had PCS lasting longer than 6 days (area under the receiver operating characteristic curve = 0.91) compared with nonconcussed players. What we all want, of course, is high diagnostic accuracy separating concussed individuals

who recover quickly from those who have persistent symptoms. This remains a goal for future studies.

This study casts serious doubts on the usefulness of NSE and S-100B as TBI biomarkers, at least for mild injuries. The NSE concentration was not elevated after a concussion compared with the preseason baseline. The S-100B concentration was elevated immediately after a concussion but normalized by 12 hours after injury. More importantly, levels of both NSE and S-100B were elevated after a friendly match that did not result in concussion (presumably a consequence of exertion and bruising of muscles and peripheral tissues), indicating a lack of specificity for brain injury.

There are some important limitations of this study. The sample size is relatively small, and replication in a larger cohort is in order. More importantly, the length of follow-up is relatively short. It is critical to know how long it takes for plasma total tau levels to normalize after an index mTBI or if there is some stage at which tau remains persistently elevated. Future studies should address whether elevated plasma tau identifies athletes who have sustained multiple mTBIs and are at risk for developing chronic traumatic encephalopathy. Finally, tau is a measure of axonal injury, and TBI is a heterogeneous disorder affecting all cell types in the brain. It is likely that biomarker panels measuring tau as well as other proteins that reflect astrocytic, endothelial, and microglial pathobiology will ultimately be required for blood biomarkers to fulfill their promise in the clinical management of TBI.[6]

ARTICLE INFORMATION

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