EDITORIAL

Blood-based biomarkers for evaluating sport-related concussion

Back in the game

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Concussion is a common problem in a wide of range of sports, particularly those involving contact, collisions, or falls. Rates of concussion have increased in collegiate level sports[1] likely due in part to improved recognition of injury or reporting of symptoms by athletes. The diagnosis and clinical assessment of concussion, however, remains challenging, largely because of the variable clinical presentation and absence of a reliable direct biomarker of injury and recovery.[2]

Following concussion, the majority of athletes recover clinically within a period of 7–10 days,[3] although recovery can take longer in certain groups such as children or adolescents.[4] A subset of athletes may develop prolonged symptoms or cognitive deficits (e.g., chronic headache, dizziness, depression, mood swings, memory loss, and executive dysfunction). Concussion or recurrent head trauma may increase the risk of mental health problems[5] or cumulative deterioration in cognitive function (e.g., chronic traumatic encephalopathy).[6] At present, the risk factors for complications following concussion remain unclear. The current expert consensus holds that premature return to play may increase the risk of adverse outcomes.[7] Critical components of clinical management of concussion therefore include making a timely and accurate diagnosis on the sidelines, removing the athlete from play, and ensuring that the athlete has recovered adequately before allowing him or her to return to play. The National Collegiate Athletic Association in the United States currently follows return to play guidelines based on expert consensus.[7] At the same time, ongoing research aims to determine whether objective measures of injury severity can inform decisions surrounding return to play.

In this issue of *Neurology*®, Gill et al.[8] report on plasma tau, a biological marker that may assist diagnosis and inform return to play decisions. Tau is a constituent of long, thinly myelinated axons, which are suspected of being vulnerable to concussion injury. While normally measured in CSF, tau measured in blood could provide the opportunity to assess neurologic injury shortly after concussion, as well as facilitate monitoring of recovery over time. The study included concussed and nonconcussed student athletes from a variety of sports (American football, soccer, basketball, hockey, and lacrosse). Control participants included a group of nonathletes who had never sustained a prior head injury. Blood samples were collected from athletes during preseason, then again at 6 hours, 24 hours, 72 hours, and 7 days after sustaining a sport-related concussion. Nonconcussed athletes and nonathlete controls provided blood samples over the same time intervals. The study included both women and men.

Looking only at those athletes who sustained a concussion, those with a longer return to play had higher tau concentrations overall, as well as an acute increase in plasma tau levels (significant at the 6-hour postconcussion mark), compared to those athletes with a short return to play. These findings are similar to a study of Swedish ice hockey players, where plasma concentrations of total tau (T-tau) assessed after concussion correlated with the number of days that it took for concussion symptoms to resolve and athletes to return to play.[9] These 2 studies taken together suggest that plasma tau might inform decisions regarding time to return to play. However, when Gill et al. compared athletes to nonathlete controls, they observed that both athlete groups (concussed and nonconcussed) had higher plasma tau concentrations compared to nonathlete controls at all time points. Further complicating the picture, tau levels among the concussed athletes showed an interesting pattern of change, whereby concussed athletes actually showed lower plasma tau levels at the 24- and 72-hour mark after concussion when compared to their nonconcussed companions who were still engaged in sports play. These findings, together with variability across players and fluctuation in plasma tau levels over time observed in traumatic brain injury (TBI) more generally,[10] make the use of plasma tau levels as biomarkers in concussion management more complicated. Development of cut-points for abnormal plasma tau levels may present a particular challenge if concentrations vary among players at baseline as well as over time.

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Why do student athletes have higher plasma tau? The authors speculate that physical exertion might account for the higher levels. However, Shahim et al.[9] did not find that physical exertion affected plasma T-tau concentrations in ice hockey players assessed before and after a friendly hockey game (free of concussions). The authors also note that subconcussive hits may play a role in maintaining elevated tau in the athlete controls. In addition, tau measured in plasma may reflect both CNS and peripheral nervous system origins. The relationship between plasma levels of tau and central measures is still relatively understudied, and plasma tau may only partly reflect brain pathology.

Overall, this study and others in TBI support an emerging picture of elevated plasma tau, especially among players who experience more serious concussion as indexed by longer return to play. The findings may also inform the biology of concussion, supporting the idea that axonal injury is a feature of sport-related concussion. This study and others conducted in the sports setting open the door for further evaluation and possible future implementation of blood-based biomarkers for evaluation of concussion. Nevertheless, more work is needed before blood-based biomarkers can be used for management of sport-related concussion.

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