Biomarkers, Genetics, and Risk Factors for Concussion

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Abstract: It is estimated that between 1.6 and 3.8 million concussions occur annually in the United States. Although frequently regarded as benign, concussions can lead to multiple different adverse outcomes, including prolonged postconcussive symptoms, chronic traumatic encephalopathy, cognitive impairment, early onset dementia, movement disorders, psychiatric disorders, motor neuron disease, and even death. Therefore it is important to identify individuals with concussion to provide appropriate medical care and minimize adverse outcomes. Furthermore, it is important to identify individuals who are predisposed to sustaining a concussion or to having an adverse outcome after concussion. This article will discuss the current research on serum biomarkers for concussion, genetic influence on concussion, risk factors associated with concussion predisposition and poor outcome, and practical suggestions for the application of this information in clinical practice.

INTRODUCTION

The Centers for Disease Control and Prevention previously estimated that approximately 300,000 concussions occur annually in the United States [1]. However, this estimate was based on persons who reported a loss of consciousness associated with the concussion. Because loss of consciousness only occurs in approximately 8%-19% of sports concussions, a more accurate estimate is 1.6-3.8 million concussions per year [2,3]. Even this estimate may be low, because results of several studies suggest that athletes frequently do not report sustaining a concussion because of a lack of concussion recognition or to avoid exclusion from sports [4-6]. It is apparent that concussions are a common occurrence in the United States.

Although the common misconception that concussions are not serious injuries continues to exist, mounting evidence indicates that the structural and clinical sequelae associated with concussions are significant [7-10]. Concussions are the consequence of a direct or indirect blow that results in a sudden angular acceleration or deceleration of the brain tissue within the calvarium [11]. Diffuse shear and strain forces occur, which cause variable degrees of injury to neurons, glia, and vascular structures [11]. Axons are particularly susceptible to damage, which often begins with disruption of cytoskeletal elements and impairment of axonal transport and cellular functions [12]. Delayed cytoskeletal damage may result from activation of intracellular proteases called calpains [13], and proteins such as amyloid precursor protein accumulate at the injury site [12]. In addition, at the time of the initial injury, voltage-dependent potassium channels open, which causes an efflux of potassium into the extracellular space. Metabolic demand is increased when the adenosine triphosphate–dependent sodium-potassium pump is activated to reestablish the normal resting membrane potential. The excitatory neurotransmitter glutamate also is released at the time of injury. Glutamate can bind to a number of receptors including N-methyl-d-aspartate receptors. When glutamate binds to the N-methyl-d-aspartate receptor, intracellular calcium levels increase. The neuron attempts to contain the calcium by sequestering it within the mitochondria. However, increased calcium concentrations within the mitochondria inhibit mitochondrial function and may lead to mitochondrial swelling and rupture and, potentially, cell death either via necrosis or apoptosis [11].
Although microstructural injury is theorized to accompany all concussions, several potential clinical outcomes may occur after concussion. Most commonly, postconcussive symptoms resolve within a short period (7-10 days), and the athlete is able to resume sports participation without sequelae after completion of a graduated return-to-play protocol [14]. However, some athletes do not have such a favorable outcome. Persistent postconcussive symptoms, referred to as the postconcussion syndrome, may develop [15]. The catastrophic injury that can occur when an athlete who has not recovered from an initial concussion sustains a subsequent blow to the head is called the second impact syndrome, which universally results in either significant morbidity or death [16]. Finally, concussions have been linked to long-term complications, including chronic traumatic encephalopathy, cognitive impairment, early onset dementia, movement disorders, psychiatric disorders, and, potentially, motor neuron disease [7,17-19]. Based on the available evidence, concussions not only result in structural damage to the brain but also may cause clinically significant adverse outcomes, including death, and thus should be considered a significant injury.

One of the main difficulties that faces clinicians who evaluate and treat athletes with concussion is identifying with certainty who has sustained a concussion, who is at risk for an adverse outcome after a concussion, and when an athlete can safely return to play after a concussion. Although some athletes present with definitive signs or symptoms of a concussion, such as a loss of consciousness after a concussive injury, many studies have provided information regarding sensitivity for concussion (3%-10% for CT and 10%-57% for magnetic resonance imaging) because they primarily detect major structural changes that do not occur with concussions [11]. Therefore multiple studies have been conducted to identify serum biomarkers that can offer superior diagnostic and prognostic information related to concussions. Furthermore, many studies have provided information regarding risk factors that predispose athletes to concussion and adverse outcomes related to concussion. The remainder of this article will discuss the current research on serum biomarkers for concussion, genetic influence on concussion, risk factors associated with concussion predisposition and poor outcome, and practical suggestions for the application of this information in clinical practice.

BIOMARKERS

After brain injury, proteins leak from damaged neurons and supporting cells into the cerebrospinal fluid, where they can potentially cross the blood-brain barrier and enter the peripheral circulation. Proteins derived from neurons include neuron-specific enolase (NSE) and cleaved \( \tau \) protein (CTP) [20]. Proteins from glial cells include S-100 proteins, creatine kinase \( \beta-B \), glial fibrillary acidic protein, and myelin basic protein [11,20]. Although all of these serum biomarkers have the potential to provide useful information in the setting of a concussion, only S-100B, NSE, and CTP actually have been studied in this population, and most of the studies did not specifically evaluate patients with concussion but rather patients with mild traumatic brain injury. The definition of mild traumatic brain injury varies, depending upon the study, but frequently includes a Glasgow Coma Scale score of 13 or higher, the absence of focal neurologic deficits, and loss of consciousness that lasted less than 15 minutes. Based on this definition, concussion is one type of mild traumatic brain injury.

**S-100\( \beta \)**

The S-100 group of proteins are acidic, calcium-binding astrocyte proteins with a molecular weight of approximately 21 kDa. Human brain tissue has 2 isoforms: beta-beta (\( \beta-B \)) referred to as S-100\( \beta \), and alpha-beta (\( \alpha-B \)) referred to as S-100\( \alpha \). Although it was once thought that S-100 proteins were isolated to brain tissue, S-100\( \beta \) has been identified in many other tissues, such as cartilage and skin. The S-100 group appears to play a regulatory role in neuronal proliferation, differentiation, regeneration, and apoptosis [20,21].

A wide variety of serum S-100\( \beta \) assays are available, with newer assays being more sensitive. When taken within 4 hours of mild traumatic brain injury, older serum S-100\( \beta \) assays were elevated in 17%-35% of patients with mild traumatic brain injury [22-24], whereas newer assays are reportedly elevated in 38%-71% of patients with mild traumatic brain injury [25-27]. Despite the increased sensitivity of newer serum S-100\( \beta \) assays, the sensitivity and specificity (61% and 77%, respectively) for mild traumatic brain injury remain suboptimal [28]. In addition, elevated levels of S-100\( \beta \) have been demonstrated in athletes without concussion who are participating in soccer, basketball, and hockey [29-33]. Patients with medical conditions such as Alzheimer disease, multiple sclerosis, Down syndrome, and schizophrenia also can demonstrate elevated levels of S-100\( \beta \) [34-37]. Thus the specificity of S-100\( \beta \) for concussion is lacking.

Several studies have evaluated the ability of S-100\( \beta \) levels to predict abnormal head CT scans in the acute setting [24,38-49]. A recent meta-analysis determined that postconcussion elevations of S-100\( \beta \) of higher than 0.10 \( \mu \)g/L were 75%-100% sensitive for predicting an abnormal head CT scan [50]. Furthermore, S-100\( \beta \) levels lower than 0.10 \( \mu \)g/L had a negative predictive value of 90%-100% for predicting a normal head CT scan. Therefore S-100\( \beta \) levels may be used...
to assist clinicians in emergency settings to determine when to order a head CT scan in athletes with a concussion.

Evidence of the ability of S-100 to provide prognostic information in patients with mild traumatic brain injury is conflicting. Five studies have demonstrated an increase in the incidence of persistent postconcussive symptoms in patients with mild traumatic brain injury who have elevated S-100 levels [23,25,51-53]. The studies of Townend et al [51] and Stranjalis et al [53] demonstrated that S-100 levels higher than 0.48 ng/L after concussion were more than 75% sensitive and specific for predicting worse functional outcomes 1 week (Stranjalis et al [53]) to 1 month (Townend et al [51]) after injury. However, multiple other studies have found no correlation between elevated S-100 levels and persistent cognitive abnormalities or postconcussive symptoms after a mild traumatic brain injury [24,41,54-57]. The findings of these studies suggest that S-100 can assist with predicting an abnormal head CT scan, but its ability to predict functional outcomes and the development of postconcussive symptoms is less clear. Furthermore, S-100 is not sensitive enough to assist with the diagnosis of mild traumatic brain injury at this time.

**NSE**

NSE is a 78 kDa glycolytic protein that is located primarily in the neuronal cytoplasm. It assists in the elevation of intraneural chloride concentrations during nerve excitation. Although primarily located in nerves, NSE also has been found in smooth muscle, adipose tissue, platelets, and red blood cells [21]. NSE has been evaluated as a marker for mild traumatic brain injury in a number of studies. Similar to S-100, the sensitivity of NSE for mild traumatic brain injury is highly variable, ranging from 40%-89% [21,25,58,59]. Furthermore, elevated postconcussive levels of NSE do not appear to predict persistent postconcussive symptoms [21,25,59]. Based on the available evidence, NSE does not have adequate sensitivity to assist with diagnosis of mild traumatic brain injuries, nor does it provide significant prognostic data related to mild traumatic brain injuries.

**Cleaved \(\tau\) Protein**

\(\tau\) is a microtubule-associated structural protein located within axons. After brain injury, \(\tau\) is proteolytically degraded. One of the resulting byproducts is CTP. Cerebrospinal fluid elevations of CTP have been identified in patients with moderate to severe traumatic brain injury [60,61]. One study found that detectable serum CTP after moderate to severe traumatic brain injury was 53% sensitive and 91% specific for predicting intracranial injury [62]. Detectable serum CTP also was 64% sensitive and 82% specific for predicting a poor outcome, defined as either dying in the hospital or requiring nursing home placement after discharge from the hospital [62].

Four studies have evaluated the ability of serum CTP to diagnose mild traumatic brain injury or predict prolonged postconcussive symptoms after mild traumatic brain injury [55,63-65]. Unfortunately, no difference in the presence or absence of serum CTP between patients with mild traumatic brain injury and control subjects has been demonstrated [63,65], nor does CTP appear to provide any prognostic information related to prolonged postconcussive symptoms [55,65]. Finally, the presence of serum CTP does not predict abnormal findings on head CT scans in patients with mild traumatic brain injury [64,65]. Based on the available evidence, CTP does not provide diagnostic or prognostic information in the setting of mild traumatic brain injury. Furthermore, CTP does not enhance the ability to determine when a head CT should be ordered in the setting of mild traumatic brain injury.

**Genetics**

It has been hypothesized that outcomes after traumatic brain injury may be genetically influenced [66]. Several genes have been studied in athletes with concussion or mild traumatic brain injury, including APOE and \(\tau\) genes.

**APOE**

The APOE gene is located on chromosome 19 at position q 13.2, the transcription of which results in the production of apolipoprotein E (Apo E) [67]. Three major APOE alleles (\(e2\), \(e3\), and \(e4\)) code for 3 Apo E isoforms [67]. Apo E assists with lipid transport in the brain, maintaining neural integrity, and recovery after a brain injury [68]. Apo E production increases postbrain injury, and although the \(e3\) allele promotes neurite outgrowth, \(e4\) inhibits it. Apo E-\(e4\) is a risk factor for Alzheimer disease [69], chronic traumatic encephalopathy in boxers [70], and worse functional and cognitive outcomes after severe traumatic brain injury [66,71], and it may modify the type and severity of brain damage from a severe traumatic brain injury [66].

Several studies have evaluated Apo E-\(e4\) in the setting of concussion or mild traumatic brain injury. Kristman et al [72] identified the Apo E-\(e4\) allele in 318 of 822 collegiate student athletes evaluated over a 4-year period. The athletes were monitored prospectively for the occurrence of a concussion. After controlling for age, gender, weight, height, and sports, the researchers found that athletes with Apo E-\(e4\) did not have an increased risk of concussion when compared with those without this Apo E allele. Three studies revealed no correlation between the presence of Apo E-\(e4\) and poor outcome after mild to
moderate traumatic brain injury in pediatric [73] and adult patients [74,75].

G-219T polymorphism in the APOE promoter region increases post-traumatic brain injury levels of Apo E and is a risk factor for Alzheimer disease [76] and poor outcome after moderately severe traumatic brain injury [77]. A study by Terrell et al [78] demonstrated a 3-fold increase in risk for a history of concussion in athletes with the G-219T-TT genotype when compared with the G-219T-GG genotype in the APOE promoter region, which suggests that the APOE promoter G-219T-TT genotype may predispose to concussion. However, no prognostic information was collected in this study.

Based on the available evidence, the presence of the Apo E-ε4 allele does not appear to predispose to concussion or prognosticate a worse outcome. However, results of preliminary research suggest that APOE promoter G-219T-TT may predispose to concussion, but further research is required to corroborate this finding.

Table 1. Concussion risk factors

<table>
<thead>
<tr>
<th>Predisposed to Concussion</th>
<th>Prognosticate Poor Outcome</th>
<th>Increase Risk of Catastrophic Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Female gender</td>
<td>1. Female gender</td>
<td>1. Young age (&lt;18 y)</td>
</tr>
<tr>
<td>2. Fatigue</td>
<td>2. Prior concussion</td>
<td>2. Recent history of concussion</td>
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<tr>
<td>4. Ser53Pro polymorphism*</td>
<td>4. Preconcussion learning disorder</td>
<td></td>
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<tr>
<td>5. APOE promoter G-219T-TT*</td>
<td>5. Preconcussion migraine headaches</td>
<td></td>
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<td></td>
<td>6. Post-traumatic amnesia</td>
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<td></td>
<td>7. Younger age (high school &gt; college &gt; professional athletes)</td>
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<td></td>
<td>8. Excessive postinjury exercise</td>
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*Possible risk factor but requires more research to confirm.

Concussion risk factors

Risk factors can be divided into 3 groups: those that predispose to concussion, those that prognosticate delayed recovery, and those that increase the risk of catastrophic injury (Table 1). Risk factors that predispose to concussion include female gender (the concussion rate is approximately 2-2.5 times higher in females than in males) [3,80-89], fatigue from physical exertion (possibly due to slowed reaction time, dehydration, and higher metabolic demands) [90,91], and history of previous concussion (athletes with concussion are 3 times more likely to sustain a concussion during the same season) [92]. Furthermore, a study by Delaney et al [93] demonstrated that athletes who sustained a concussion with a loss of consciousness sustained a subsequent concussion 6 times more frequently than did athletes with a prior concussion who did not experience a loss of consciousness.

Multiple factors increase the risk of a poor outcome after concussion. Female athletes tend to have more initial symptoms and take longer to recover after concussions than do male athletes [94-97]. Athletes with a history of concussions, particularly 3 or more concussions, are at increased risk for developing postconcussion syndrome [38,98] and cognitive impairments [17]. A premorbid history of anxiety or depression increases the risk of postconcussive fatigue, depression, anxiety, and subjective cognitive complaints, but it is unknown whether they increase concussion susceptibility [99]. Because concussions frequently result in decreased attention and difficulties with memory and learning, athletes with a baseline learning disorder may experience an exacerbation of their learning disorder after a concussion [99]. Pre-existing learning disorders also complicate postconcussion management because of the difficulties of interpreting neuropsychological testing if baseline neuropsychological testing was not performed (ie, what abnormalities are new and which ones were pre-existing). It takes longer for athletes with a preconcussion history of migraine headaches to recover from a concussion [100]. Athletes with larger postconcussive symptom loads and delayed recovery times are 10 times more likely to have reported retrograde amnesia and 4 times more likely to have experienced anterograde amnesia at the time of their concussion [2,101]. Concussion recovery duration is inversely correlated with age (ie, younger age is associated with slower recovery) when comparing high school, collegiate, and professional athletes [102-104]. Athletes who per-
form high levels of exertion (defined as school activity and participation in a sports game) after a concussion have delayed recovery and perform worse on postconcussion computerized neuropsychological testing \[105\]. Finally, although no studies have directly evaluated the susceptibility of children to concussion or the long-term sequelae related to concussions in pediatric athletes, many experts suggest that care should be taken when managing this population because of the complexity of the developing brain and the difficulties of reliably evaluating the pediatric athlete with a concussion \[99,106\].

The most significant adverse outcome from concussion is death, which is usually caused by dysautoregulation of the cerebrovasculature, with simultaneous catecholamine-induced hypertension that leads to fatal malignant brain edema \[16\]. Postmortem examination of this injury reveals extensive cerebral edema without a space-occupying hematoma \[16\]. Although a severe initial head injury can result in this fatal scenario, it more commonly occurs in athletes with a recent history of concussion who sustain a subsequent, and often mild, concussive event while still symptomatic from the initial concussion \[16\]. Thus it often is referred to as “second impact syndrome.” \[107\]. Although second impact syndrome is surrounded by controversy and its incidence and prevalence are unknown, unquestionably, identifiable cases of second impact syndrome occur yearly \[16\]. Therefore risk factors for second impact syndrome should be recognized by medical professionals, and their presence should influence the return-to-play decision-making process. Risk factors include young age (18 years or younger), recent concussion, and continued postconcussive symptoms. Any patient who meets these criteria should not be allowed to return to sports until the symptoms have resolved.

**CLINICAL IMPLICATIONS AND CONCLUSIONS**

It is well known that each concussion is unique and can result in a variety of clinical outcomes that range from rapid symptom resolution to death. Any diagnostic or prognostic information that can be obtained is important when managing athletes with concussion. Unfortunately, at this time, biomarkers have only a limited role in the management of concussion. In particular, S-100\(\beta\) may be used to assist emergency department physicians in determining whether to order a head CT scan of athletes with concussion. In addition, genetic testing has no current role in concussion management. However, the clinical value of concussion risk factors is significant. If sports medicine clinicians can identify athletes at risk for sustaining a concussion or having a poor outcome after concussion, then an intervention possibly can be implemented and can lead to a decrease in concussion incidence and severity. Although many of the risk factors listed in this article are not modifiable (eg, gender and age), actions still can be taken with this information, such as counseling athletes who are at risk for concussion, advocating for appropriate sports rule enforcement and rule changes to increase the safety of sports participation, and preventing catastrophic injury by disallowing any athlete with a recent concussion and with persistent postconcussive symptoms from returning to sports until the symptoms have resolved. Therefore it is important for sports medicine clinicians to be familiar with concussion risk factors and to recognize their clinical significance.

**REFERENCES**