From Concussion to Chronic Traumatic Encephalopathy: A Review

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Sports-related activities account for an estimated 10% of head and spinal cord injuries. In recent years, concussion in particular has garnered more interest in the medical field as well as the media. Reports of athletes suffering from long-term cognitive deficits and Parkinsonian symptoms have sparked concern in a disease process that has often been underestimated or ignored. As more reports surface, the desperate need for a better understanding of the neuropathology has been made clear. In addition to the concern for acute injury, long-term sequelae such as chronic traumatic encephalopathy (CTE) are feared consequences of concussive injuries. Research studies have shown significant overlap in the neuropathology between CTE and chronic neurodegenerative processes such as Alzheimer’s disease (AD). In particular, tau protein deposition has been found to be present in both disease processes and may play an important part in the clinical findings observed. The present review discusses concussion and our current understanding of pathological findings that may underlie the clinical features associated with concussive injuries and resulting chronic traumatic encephalopathy.

Keywords: chronic traumatic encephalopathy, concussion, sport, neuropsychology, traumatic brain injury

First described by Martland in 1928, chronic traumatic encephalopathy (CTE) is characterized by confusion, tremors, and slowing of speech, as well as Parkinsonian symptoms and overall mental deterioration. While this condition was originally
thought to only affect boxers who had suffered repeated blows to the head, more recently it has been suspected that CTE may not be limited to boxers only. This suspicion gained confirmation in 2005, when the first case of CTE in a National Football League (NFL) player was reported (Omalu et al., 2005). Unfortunately, we are only now beginning to understand its pathophysiology, and definitive treatment options are not yet available. Furthermore, diagnostic tools are limited, which is why confirmation can only be obtained at autopsy. Since CTE is thought to be caused by repeated concussive injuries, improving our understanding of concussion will help us develop prevention and treatment strategies.

It is currently estimated that sport-related activities account for 10% of head and spinal cord injuries (Flanagan & Bailes, 1998). Each year, about 1.5 million Americans sustain traumatic brain injuries (TBI) without noted loss of consciousness and without any need for hospitalization. About the same number of Americans suffers TBI with impairment of consciousness but without need for long-term hospitalization (DeKosky, Ikonomovic, & Gandy, 2010). The Center for Disease Control and Prevention (CDC) attributed 207,830 emergency room visits per year between 2001 and 2005 to nonfatal sport-related head injuries (CDC, 2009). These statistics indicate that sport-related head injuries pose a serious public health issue. In recent years, greater efforts have aimed to educate parents, athletes, coaches, and the general public on signs and symptoms of concussion and its potential long-term sequelae. For example, the CDC has published media kits for parents, athletes, and coaches to raise awareness and improve the detection of concussion.

In the United States, concerns about sport-related injuries date back to President Teddy Roosevelt. He was among the first to appreciate the health issues associated with contact sports. After 19 athletes were killed or paralyzed playing football, he called for rule changes to improve safety (Dunn, Dunn, & Day, 2006). As a result of his initiative, the National Collegiate Athletic Association (NCAA) was formed, resulting in implementation of stricter regulations to increase player safety and reduce sport-related head injuries. Some innovations that came from these regulations were to ban gang tackling and mass formations and to allow forward passing; however, despite these changes, sport-related head injuries remain high and appear to on the increase (Langlois, Rutland-Brown, & Wald, 2006).

A study looking at high school athletes in 10 different sports over a 3-year period revealed that all were at risk for concussive injuries. The data showed that 63% of concussions occurred in boys’ football, 10% in wrestling, 6% in soccer, and the rest in basketball, softball, baseball, field hockey, and volleyball (Powell & Barber-Foss, 1999). In another study, Gessel et al. showed in 2007 that while football had indeed the highest concussion rate among high school students, rates were still high among partial contact sports such as soccer (Gessel, Fields, Collins, Dick, & Comstock, 2007).

There have been three international conferences on concussion in sports since 2001: Vienna in 2001, Prague in 2004, and Zurich in 2008. The goal of these conferences was to establish a working definition of concussion as well as to determine prevention and treatment strategies (Aubry et al., 2002; McCrory et al., 2005, 2009). In addition, according to PubMed Central, more refereed publications on sport-related concussion have been published since 2000 than in all previous years combined (Cantu, 2009). Increased attention has not only been limited to scientific advancements. In recent years, the topic has also gained significantly more media
attention, as high profile athletes have come forward to share their experiences and struggles with concussion.

Due to the popularity of contact sports, prevention of all concussions is impossible, but it is imperative to limit the number of repeat injuries athletes sustain and, more importantly, improve our knowledge of the disease process. Understanding the cellular and molecular basis of concussion and CTE will hopefully lead to prevention and treatment options.

Defining Concussion

In 2008, during the third international conference on concussion held in Zurich, a panel of experts agreed on a working definition of concussion as “a complex pathophysiological process affecting the brain induced by traumatic biomechanical forces” (McCrory et al., 2009, p. 142). This can be caused by a direct blow to the head or an impulsive force that leads to acceleration of the head without direct blunt trauma to the cranium. Contrary to common belief, loss of consciousness usually does not occur, and the absence of a reported loss of consciousness does not preclude the diagnosis of concussion. In fact, it is estimated that 90% of sport-related concussions occur without loss of consciousness (Cantu, 1996). In the majority of cases, the acute clinical findings are transient and resolve spontaneously. The most common signs and symptoms are headaches, dizziness, confusion, disorientation, and blurred vision. In 2000, Guskiewicz et al. reported the rate of loss of consciousness and headaches in 1,019 cases of concussion injuries as 8.9% and 86%, respectively (Guskiewicz, Weaver, Padua, & Garrett, 2000). Finally, concussions do not produce structural abnormalities that can be detected with available imaging modalities (McCrory et al., 2009).

From a biomechanical standpoint, acceleration-deceleration forces and linear and especially rotational forces have been implicated in causing concussive injuries (Ommaya, 1995). Depending on the severity of impact, the individual may sustain a coup or contracoup injury. In a coup injury, the damage occurs at the site of impact, while a contracoup injury leads to brain injury on the side opposite the impact (Sano, Nakamura, Masuzawa, & Hashizume, 1967).

Prevention

Though desirable, prevention of all serious concussive injuries is an unrealistic goal, particularly in contact sports. Nevertheless, it is an important goal, as epidemiological studies indicate that the first concussion may increase the likelihood of a second concussion by up to threefold (Guskiewicz et al., 2000). Considering that repeat injuries may be more severe than the initial one, and that the likelihood for long-term neurological deficits are increased with repeat injuries and in rare cases may be fatal, prevention becomes even more essential.

One common preventative measure is the use of headgear such as helmets and mouth guards. However, while such protective headgear has long been recommended for contact sports, its effectiveness in preventing concussion still has not been clinically proven. For example, helmets help prevent skull fractures and
direct injury to the head, but they have not been shown to prevent concussions, even
though they lessen the impact that is being transmitted to the brain itself. Mouth
guards have also not been shown to reduce or change the incidence of concussions;
however, they can prevent oro-facial and dental injuries. Interestingly, there is
concern that protective equipment can result in more aggressive play and therefore
paradoxically may increase the incidence of injuries (Hagel & Meeuwisse, 2004).

Even though protective gear continues to have shortcomings and may not fully
prevent head injuries, screening questions regarding their proper and consistent use
should be incorporated in routine clinic visits. Not only should the equipment fit
properly, but it also needs to meet the National Operating Committee on Standards
for Athletic Equipment (NOCSAE) or American Society for Testing and Materi-
als (ASTM) standards (Guskiewicz et al., 2004). It is important that regulations
be established that ensure adherence on both the professional and amateur levels.

In 2005, the CDC implemented a national concussion awareness and education
initiative in collaboration with the Children’s Health Act of 2000. As part of this
initiative, multimedia tool kits entitled “Heads Up: Concussion in High School
Sports” were developed for high school coaches and certified athletic trainers and
directors. In addition to raising awareness and providing educational materials,
the objective of the initiative was to allow coaches a means to inform others on
the subject matter and to help them develop the skills to screen for and recognize
concussion among their athletes (CDC, 2009). According to a follow up study
conducted by the CDC, this program led to a positive change in knowledge base,
attitudes, behaviors, and skills toward concussion awareness. Most importantly, the
tool kit solidified the understanding that concussion is a serious injury and needs
to be addressed appropriately (Sarmiento, Mitchko, Klein, & Wong, 2010). The
study also confirmed that there remains skepticism among athletes, their parents,
and coaches of the seriousness of concussions and a tendency toward downplay-
ing its effects. Recently, a number of states have enacted legislation regarding
concussion education and qualification for who can return an athlete to play after
sustaining a concussion.

Evaluation

To ensure proper management of an injured athlete, it is important to perform a
proper evaluation in a timely fashion. Since evaluations are not limited to the side-
lines but may also occur in an outpatient setting, all individuals who may be exposed
to injured athletes should be aware of the wide range of mechanisms that can lead
to concussive injuries. This will allow for prompt assessment, correct diagnosis,
and proper management. Imaging should be obtained if potential neurosurgical
emergencies are suspected, such as acute subdural or epidural hematomas.

Several screening tools have been proposed for the management of sport-related
concussion. It is important that such screening tools have features that make them
easy and efficient to use in emergent situations. Proper and swift screening trans-
lates into expeditious and appropriate management of the injury and may prevent
further damage, such as CTE or a possibly fatal second impact injury. In addition,
effective screening tools will enable practitioners to monitor athletes long-term and
determine rate of recovery or worsening. During the second international conference
on concussion in sports in Prague in 2004, the Standardized Concussion Assessment Tool (SCAT) was developed. The tool drew from previous existing methods such as the Standardized Assessment Tool for Concussion (SAC), the American Academy of Neurology assessment tool, and the Sideline Concussion Check (Kelly et al., 1991; Kelly & Rosenberg, 1997; McCrea, 2001; McCrea et al., 1998). In 2008, this new assessment tool was then revised into the SCAT2.

The SCAT2 consists of eight parts, which include signs and symptoms such as cognitive ability, balance, and coordination; the Glasgow coma scale (GCS); and the Maddocks score, which uses recall of events to assess an individual for concussion. It is recommended that with the exception of the Maddocks score, the assessment should be performed continuously until the individual’s condition is found to be stable (McCrory et al., 2009). Any changes in the score may indicate worsening or improvement of the athlete’s condition. This screening tool should not be the only form of evaluation for serious injuries; however, once life-threatening injuries are ruled out, the SCAT2 may assist in quickly identifying individuals with concussion.

Since functional capacity varies greatly among individuals, baseline neuropsychological and SCAT2 testing is essential in determining the severity of the injury and for making return-to-play decisions. When possible, these should be obtained before any head injury. A recent study on baseline SCAT2 scores showed that male athletes, 9th graders, and athletes with a self-reported concussion history scored significantly lower than female athletes, upper classmen, and nonconcussed teens (Valovich McLeod, Bay, Lam, & Chhabra, 2012). In addition, athletes may intentionally try to lower their baseline scores on computerized tests such as ImPACT to minimize time off from injury, although the majority who attempt to do so can be detected by the software package (Erdal, 2012). Given these issues around baseline testing, and often significant external pressure to return an athlete, the clinician must use his or her own common sense when making judgments. In general, erring on the side of caution is likely the best advice.

It should be stated that while evaluations during an ongoing game need to be efficient and focused on the injury at hand, evaluations in an office setting require more detail. It is important to obtain a complete history, including prior injuries that may have been too minor to require medical attention; family history of migraines; learning disabilities; ADD/ADHD; anxiety; mental illness; and/or depression, as these may all be important predictors of outcome from concussion (Herring et al., 2006).

**Chronic Traumatic Encephalopathy (CTE)**

The importance of concussive injuries is undermined by the often fleeting or undetectable symptoms following the immediate injury. Unlike other forms of traumatic brain injury, concussion lacks clearly defined signs or symptoms or diagnostic modalities such as routine brain imaging. It is therefore easy to brush off a potential injury as a minor transient event without any long-term repercussions. There is mounting evidence, however, indicating that even though a concussion can initially be a minor event without any immediate observable consequences, over time and with repeated injuries, it can lead to significant disabilities and possibly catastrophic outcomes. In fact, it has been shown that following a single mild TBI,
there are changes in normal cerebral function involving metabolism, hemodynamics, and structure. These changes are believed to place the brain at higher risk for more serious damage with repeat injury (Barkhoudarian, Hovda, & Giza, 2011).

Initially termed “punch drunk,” the symptom constellation of CTE was first described by Martland in 1928. The name was later revised to “dementia pugilistica,” emphasizing that the condition was originally thought to affect only boxers who had experienced repeated blows to the head. More recently, the name was changed to “chronic traumatic encephalopathy” to include sequelae from contact sports other than boxing. The condition is described as an overall mental deterioration with Parkinsonian symptoms, including confusion, tremors, and slowing of speech. The onset of CTE is insidious, and affected individuals first notice deficits in attention, memory, and concentration leading eventually to confusion and disorientation. Over time, the condition progresses to dementia, poor judgment, irrational behavior, depression, and lack of insight. In advanced cases, Parkinsonism may develop (Corsellis, 1989).

**Chronic Traumatic Encephalopathy (CTE) and Boxing**

Boxing has a unique standing as one of the few sports where the goal is to render the opponent defenseless and ideally unconscious through a knockout (KO). Since 688 BC when boxing was first added to the Olympic Games, the danger associated with it was recognized and led to multiple revisions of the rules and safety measures (Föerstl, Haass, Hemmer, Meyer, & Halle, 2010). Despite no longer reinforcing their gloves with iron and lead, the principal aim of the sport itself puts participants at risk for serious injuries. This risk remains higher among professional boxers compared with amateurs, as several safety measures are omitted in professional matches.

Long-term effects of repeated head injuries were first recognized and described in boxers and found to have clinical and pathological manifestations that were distinct from isolated TBIs. Two hours after a severe brain injury, increased levels of amyloid-β (Aβ) and depositions of amyloid plaques can be detected in 30% of surviving individuals (Ikonomovic et al., 2004). In comparison, repetitive head injuries were found to lead to prominent tauopathy with neurofibrillary tangles and neuropil threads, and noticeable absence of Aβ deposition. Clinically, these individuals experience acute and subacute symptoms ranging from persistent headaches to gait instability and memory impairment. A study of 632 Japanese professional boxers in 2002 revealed that about half of them continued to experience symptoms the day after a KO. In addition, 10% of those athletes complained of persistent symptoms including headaches and forgetfulness (Ohhashi et al., 2002). Interestingly, cognitive deficits were found to last longer than perceived by the subject him/herself. In their study of 82 amateur boxers, Bleiberg et al. found that following a KO, visual-spatial and mathematical exercises were significantly worse during the following two days (Bleiberg et al., 2004). Ravdin et al. found in their study of 18 professional boxers that information processing and verbal fluency was still significantly impaired 1 month after a KO, compared with baseline results (Ravdin, Barr, Jordan, Lathan, & Relkin, 2003). Of note, performances in delayed recall exercises were found to be worse among amateur boxers after training matches, during which they were required to wear protective head gear, indicating that injuries may be far worse in professional matches because head gear is generally not worn (Stojsih, Boitano, Wilhelm, & Bir, 2010). Subjects were also
found to be significantly slower in reaction time tests and multiple-choice exercises after competing in amateur matches that had to be stopped (Moriarity et al., 2004).

It has been suggested that an estimated 10–20% of professional boxers suffer from chronic deficits in motor and cognitive function as well as changes in behavior (Loosemore, Knowles, & Whyte, 2007; Rabadi & Jordan, 2001). Risk factors for long-term cognitive impairment include duration of career, number of matches, and poor defensive abilities. Among boxers who have similar boxing careers, the presence of APOE ε4 allele, a dysfunctional isoform of APOE that had previously been implicated as a risk factor for early onset Alzheimer’s disease, increases the likelihood of developing dementia pugilistica (Jordan et al., 1997). To date, 39 neuropathologically confirmed cases of CTE in boxers have been reported, with many more cases possibly remaining undiagnosed. Among athletes suffering from CTE, boxers have been found to have the longest disease duration, with case reports citing up to 46 years of symptomatic disease (McKee et al., 2009).

Chronic Traumatic Encephalopathy (CTE) in Other Sports

In 2005, Omalu et al. confirmed what many had suspected for a long time: CTE was not limited to boxers only. In their article, Omalu et al. reported the first autopsy-confirmed case of CTE in a National Football League (NFL) player who had died of atherosclerotic disease 12 years after his retirement from a 17-year career in the NFL. Interviews with family members revealed that the patient had suffered memory deficits and Parkinsonian symptoms. In 2006, Omalu et al. reported the second autopsy confirmed case of CTE in a NFL player. As in the first case, the individual had retired 12 years prior from a 14-year career in the NFL. Preceding his suicide, the patient had been diagnosed with severe major depressive disorder (American Psychiatric Association, 2000) and had multiple prior suicide attempts (Omalu et al., 2006).

Since then, a total of five cases involving football players, one involving a wrestler and one involving a soccer player have been reported. Compared with boxers, affected football players were found to be younger at time of death, with an overall shorter duration of the illness (McKee et al., 2009). Review of the cases revealed that similar to CTE in boxers, the most common symptoms were mood disorders, memory loss, paranoia, and poor insight or judgment. Sadly, four of the five cases ended in tragic deaths, including two suicides.

As more and more athletes step forward to share their experiences, it becomes clear that concussion and long-term health consequences present a much larger public health problem than previously thought. Together, these cases illustrate the devastating effects that concussion and CTE can have on overall well-being and quality of life in affected individuals, as well as shed light on the delay in manifestation of symptoms. It is these outcomes that have to be kept in mind when dealing with concussion and the call for more awareness and more aggressive management.

Pathological Findings in Chronic Traumatic Encephalopathy (CTE)

Brandenburg and Hallervorden published the first neuropathological report in 1954. In their article, they were able to demonstrate Alzheimer’s disease-like changes in a 51-year-old boxer who had suffered from delayed posttraumatic dementia.
(Brandenburg & Hallervorden, 1954). To date, multiple reports have confirmed these original findings in patients with suspected CTE.

In addition to atrophy of frontal, temporal, and parietal lobes causing an overall decrease in brain volume, gross neuropathological findings include ventriculomegaly of lateral and third ventricles, cavum septum pellucidum, and scarring of cerebellar tonsils (Corsellis, Bruton, & Freeman-Browne, 1973). On a microscopic level, cell loss is noted in the hippocampus, substantia nigra, and cerebral cortex, with advanced cases also showing neuronal cell loss in the subcallosal and insular cortices as well as the frontal and temporal cortices (McKee et al., 2009).

Similar to Alzheimer’s disease, CTE is also characterized by marked tau-immunoreactive neurofibrillary tangles (NFT) and neuropil threads (NT). This tauopathy is generally diffuse and in some cases may involve all regions of the brain indiscriminately (Omalu et al., 2006). The NFTs in CTE contain all six tau isoforms and are indistinguishable from NFTs found in Alzheimer’s disease. Interestingly, amyloid plaques, which are a hallmark of Alzheimer’s disease, have been found to be present in only 44% of cases (McKee et al., 2009). This may indicate a clear distinction between the two disease processes. In addition, while Alzheimer’s disease patients typically develop NFTs in the mesiotemporal region, this area is usually spared in CTE patients. Lastly, the NTs seen in CTE are shorter and less prominent than those found in Alzheimer’s disease (Tokuda et al., 1991).

**Chronic Traumatic Encephalopathy (CTE) and Neuroimaging**

Conventional brain imaging lacks the sensitivity needed to detect subtle changes that occur with acute concussive injuries. Unlike acute intracranial bleeds or contusions, there are no specific findings with acute concussion, which may appear completely normal in affected individuals. Magnetic resonance imaging (MRI) can be used to evaluate more chronic changes such as atrophy, white matter lesions, infarcts, and demyelination; however, these findings are nonspecific (Casson et al., 1984; Corsellis, Bruton, & Freeman-Browne, 1973).

More recently, there has been interest in the use of diffusion tensor imaging (DTI) to evaluate for microstructural changes that may occur in concussion. In 2006, Zhang et al. looked at the MRIs of 49 professional boxers using conventional MRI and MR diffusion images. While these subjects had normal or nonspecific white matter findings on conventional MRIs, diffusion anisotropy analysis showed a consistent decrease in the average diffusion constant as well as the whole brain diffusion constant. These changes in regional anisotropy may indicate an early response to brain injury in these athletes and could become a useful tool for detecting early structural changes as well as monitoring long-term neurological changes (Zhang, Heier, Zimmerman, Jordan, & Ulug, 2006).

**Future Directions**

Our understanding of concussion and chronic traumatic encephalopathy is still in its infancy. More research will be necessary to advance this important area of study. In addition to prospective and long-term follow-up of individuals at risk for concussion, it is important to improve our understanding of its pathophysiology, including cellular and molecular mechanisms leading to the clinical findings of TBI.
The hope is that uncovering these pathways will open the door to the development of effective prevention and treatment approaches. In addition, discovery of genetic markers that may determine individuals who are at a higher risk of suffering from concussion and its sequelae may be important in guiding young athletes. Finally, developing better ways of detecting and diagnosing concussion will hopefully lead to lowered risk of both concussion and CTE in the future.

**Conclusion**

Sports-related concussion is now well recognized as a significant public health problem with symptoms that are often ignored and with long-term sequelae that may be more serious than previously thought. There is an emerging expert consensus regarding the definition and clinical evaluation of concussion; however, to develop more programs aimed at preventing concussions and their after-effects, better education of health care professionals, coaches, and parents will be needed. Without doubt, the most dangerous late effect of concussive or subconcussive blows is CTE, which manifests as cognitive, emotional, and motor symptoms from chronic degeneration of multiple areas within the brain. The most consistent biological marker of this disease is tau protein deposition in affected areas of the brain, but most prominently in the hippocampus and mesial temporal lobe structures. It is still not clear, however, whether tau itself is neurotoxic or a marker for an as yet unidentified agent. Additional research into the pathophysiology coupled with improved understanding of concussion prevention and mitigation will hopefully help prevent current athletes and future generations of young athletes from suffering from the debilitating neurological decline of CTE.

**References**


