[Primary Care]

Counseling Athletes on the Risk of Chronic Traumatic Encephalopathy

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Context: Chronic traumatic encephalopathy (CTE) is a rare progressive neurologic disorder that can manifest as a combination of cognitive, mood and behavioral, and neurologic symptoms. Despite clinically apparent symptoms, there is no imaging or other diagnostic test that can confirm diagnosis in living subjects. Diagnosis can only be confirmed postmortem by specific histopathologic features within the brain tissue identified on autopsy. CTE represents a unique tauopathy that is distinct from other neurodegenerative diseases.

Evidence Acquisition: PubMed was searched from 1990 to 2013 for *sport concussion* and *chronic traumatic encephalopathy*. Articles were also identified from bibliographies of recent reviews and consensus statements.

Study Design: Clinical review.

Level of Evidence: Level 5.

Results: Although CTE is postulated to occur as a result of repetitive mild traumatic brain injury, the specific etiology and risk factors have not yet been elucidated, and postmortem diagnosis makes causality difficult to determine.

Conclusion: When counseling athletes and families about the potential association of recurrent concussions and the development of CTE, discussion of proper management of concussion is cornerstone. Unfortunately, to date, there is no equipment that can prevent concussions; however, rule changes and legislation may decrease the risk. It is imperative that return to play is medically supervised by a provider trained in the management of concussion and begins only once symptoms have resolved. In addition, athletes with permanent symptoms should be retired from contact sport.

Keywords: chronic traumatic encephalopathy; concussion; mild traumatic brain injury; tauopathy

A concussion is a mild traumatic brain injury resulting from direct impact to the head or indirectly via impact to the body with transmission of forces to the brain, which typically results in temporary neurologic dysfunction. This dysfunction may manifest with obvious symptoms at the time of the impact; however, as the injury evolves, symptoms may emerge hours or even days later.

Proper management of concussions, including immediate removal of athletes from play until resolution of symptoms, is imperative. Continued activity is thought to increase the risk for prolonged symptom duration.[15] Additionally, removal from play will prevent catastrophic events such as second impact syndrome, which generally results in death or severe disability.

Since the introduction of the Zackery Lystedt Law in Washington State in 2009, there has been a deluge of media attention surrounding the management of concussions, including a focus on long-term exposure to repetitive head trauma. There has been increasing concern that, even in those athletes who appear to fully recover following a concussion, there may be long-term effects on the brain after repetitive trauma. Indeed, collegiate American football players with 3 or

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more previous concussions were found to have a greater likelihood of suffering a subsequent concussion and were more likely to have symptoms for greater than 1 week.[14]

The vast majority of athletes have symptoms that last for less than 10 days following a concussion, but 10% to 15% may have prolonged symptoms.[24] In these athletes with prolonged symptoms, a small minority may go on to develop postconcussion syndrome, characterized by symptoms persisting for greater than 3 months. This is generally described as a time-limited disorder, with most achieving full recovery.[25] Up to 20% of those with prolonged symptoms may have permanent postconcussion syndrome.[25] Persistent symptoms in some athletes may represent undiagnosed depression or anxiety and should be treated in a multidisciplinary setting. In addition, there are also athletes who have symptoms of depression or memory difficulties similar to those seen in postconcussion syndrome but arise after a prolonged symptom-free period. Some assert that the presence of new mood or cognitive complaints after a symptom-free interval are a consequence of previous head injuries, while others believe that these symptoms may arise simply because of their high prevalence in the general population.[25]

Chronic traumatic encephalopathy (CTE) is a rare progressive neurological disorder that can present several years after retirement from sporting activity.[1,10] Permanent postconcussion syndrome is not thought to cause CTE, and, although the terms are sometimes incorrectly used interchangeably, they are 2 separate entities.[1]

There has been growing concern that CTE results from repetitive head trauma. The literature reveals conflicting evidence on whether a prior history of concussions leads to long-term cognitive deficits.[3,6,8,34,40] A history of multiple prior concussions has been linked to increased risk of depression[13,18] as well as self-reported mild cognitive impairment and earlier onset of Alzheimer disease[12] in professional American football players. In contrast, a study with a 50-year follow-up by Savica et al[36] did not find evidence for increased risk of dementia, Parkinson disease, or amyotrophic lateral sclerosis in former high school football players—symptoms commonly reported in athletes found to have suffered from CTE.

HISTORY OF CHRONIC TRAUMATIC ENCEPHALOPATHY

In 1928, Dr Martland[22] first described a progressive neurological deterioration in boxers who had suffered repetitive head trauma. Over time, it became clear that such deterioration was not limited to boxers but could be found in other sports as well, and, more than 60 years ago, the terms *punch drunk syndrome* and *dementia pugilistica* were replaced by "chronic traumatic encephalopathy" (CTE).[29]

Martland[22] described an intermittent flopping of a leg or foot as often being the earliest manifestation of punch drunk syndrome; this particular symptom has not been subsequently described as a symptom of CTE. This initial symptom could be followed by hesitancy of speech, tremors, and parkinsonian features. Mental deterioration and dementia developed decades later. Punch drunk syndrome was seen in aggressive boxers who used force over skill and in lesser skilled boxers who were used for training and were often knocked out more than once per day.[22]

The histopathologic changes present at autopsy in 15 former professional boxers with correlating clinical findings[7] were first described in 1973. The most striking features were a septum cavum pellucidum, degeneration of the substantia nigra with premortem parkinsonian features, and neurofibrillary tangles in the absence of neuritic plaques. The absence of plaques, in particular, differentiated this from Alzheimer dementia where plaques are quite prominent. Aggression and violence were seen in some of these men prior to their death; however, given that boxing is by nature a violent sport that attracts aggressive personalities, it was difficult to conclude that there was a direct relationship between their later behavior and their progressive neurological disease. More than half of those studied had participated in greater than 300 bouts or 15 years of professional boxing. Those men who had participated in fewer fights throughout their careers or who were amateurs as opposed to professionals seemed to have less severe disease.[7]

More recently, CTE has been described in players that have retired from the National Football League. The first case was described in 2005,[31,32] with several more later.[27-29] Many of the recent cases were involved in tragic or traumatic deaths in middle age. This is in stark contrast to the boxers studied earlier, who tended to survive into their seventh decade and beyond. The average duration of the disease in boxers was 20 years compared with only 6 years in American football players.[27] Additionally, while movement disorders tended to be common in early descriptions of CTE, behavioral and neuropsychiatric issues tend to predominate in modern cases of CTE.[25] In those who did not die from other causes, dementia manifested late in the disease.[10]

While the majority of documented cases are in professional boxers and American football players, histopathologic evidence of CTE has also been reported in individuals playing soccer, wrestling, hockey, and in other individuals who had sustained trauma relating to self-injurious behavior, abuse, and military service.[27,29] In several of these cases, however, despite pathological changes consistent with CTE noted on autopsy, athletes did not manifest clinical evidence of CTE. These incidental findings certainly present a challenge in correctly predicting postmortem findings based on clinical presentation.

PRESENTATION OF CHRONIC TRAUMATIC ENCEPHALOPATHY

Chronic traumatic encephalopathy is a distinct, progressive tauopathy that may occur as a result of repetitive mild traumatic brain injury.[29] Of note, the disease is not limited to those with a history of brain injury suffered during athletics but can also be seen as a result of abuse, military exposure, and other forms of

trauma.[1,27,29] Further risk factors beyond exposure to brain trauma currently remain unknown, though many are hypothesized.

Clinical Presentation

Clinical manifestations of CTE can be broadly categorized into cognitive, mood and behavioral, and neurologic symptoms. Cognitive changes generally include deficits in memory, attention, and executive functioning, with eventual dementia if patients survive for long enough.[1,10] Behavioral changes include impulsiveness, disinhibition, substance abuse, violence, and aggression.[1,10] Drug and alcohol abuse is common in athletes with CTE.[10] These behaviors may be the cause of some clinical symptoms of CTE, while others argue that it may instead be an effect of CTE via loss of inhibition and judgment.[10]

Mood changes often manifest as apathy, depression, irritability, and even suicidality.[1,9,10,16,17,35] Suicidality is a particularly salient symptom in modern athletes with CTE,[33] though this was not seen in the original descriptions of the disease.[7,22] Neurologic symptoms can manifest as parkinsonian symptoms or dysarthric speech. Some affected individuals can also develop chronic traumatic encephalomyelopathy, a variant of CTE with more severe neurological symptoms that clinically presents as motor neuron disease. Despite clinical similarities, this is distinct from amyotrophic lateral sclerosis.[1,28]

Chronic traumatic encephalopathy can only be diagnosed at autopsy, and therefore, there are no physical examination or neuropsychological test findings that are specific for CTE. Certainly changes in cognitive function, mood and behavior, or any neurological changes should be investigated to evaluate for other conditions such as depression or Parkinson disease that can be managed medically.

Histopathology

Distinct histopathological changes distinguish CTE from other degenerative diseases, most notably, Alzheimer dementia and frontotemporal dementia. CTE tends to preferentially affect the cerebral cortex and the medial structures of the limbic system.[1] Histopathologic changes include atrophy of the cerebral cortex, medial temporal lobe, diencephalon, mammillary bodies and brainstem, pallor of the substantia nigra, ventricular enlargement, fenestrated cavum septum pellucidum, and phosphorylated tau neurofibrillary tangles.[27] The distribution of tau pathology in CTE is in cortical laminae II and III, while it is in layer V in Alzheimer dementia. Additionally, tau pathology in CTE is seen deep in the sulci and perivascular and tends to be less uniform than in Alzheimer dementia.[10] There are 4 stages of deposition of hyperphosphorylated tau identified pathologically, thought to represent advancing stages of the disease.[29] The difficulty with this staging system is that advancing stages on autopsy did not always correlate with advancing clinical presentation. Additionally, 11% of those with histopathologic evidence of CTE were reportedly asymptomatic at the time of death.[29] As previously discussed, the presence of pathological evidence of CTE at autopsy does not always correlate with clinical symptoms consistent with CTE, and therefore, caution must be taken when attempting to determine causality. Many of the advanced cases also had significant drug and alcohol use, which may complicate the clinical presentation.[29]

Imaging

At this time, there is no way to diagnose CTE premortem. Computed tomography and magnetic resonance imaging (MRI) cannot be used to diagnose concussion and are typically reserved for cases in which it is necessary to rule out more severe brain injury. Susceptibility weighted imaging can be added to traditional MRI protocols to evaluate small hemorrhages indicative of diffuse axonal injury.[11] Functional MRI, MR spectroscopy, and diffusion tensor imaging have been used in research settings but are not yet available or recommended for routine use in evaluating concussions or diagnosing CTE.[11,25] Positron emission tomography has been studied for its usefulness in diagnosing Alzheimer disease[39] and as a possible method to evaluate tau deposition in retired National Football League athletes[38]; however, additional research is needed prior to its use for diagnosis of CTE.

PREVENTION STRATEGIES

Because CTE cannot be diagnosed until postmortem autopsy, identifying prevention strategies is a challenge. If CTE is assumed to result from repetitive concussions, then prevention of concussion would be imperative for prevention of CTE. There are several difficulties with this assumption, however. First, correlation does not equal causation, and retrospective cases do not prove that a history of multiple concussions leads to CTE. While cumulative head trauma from repeated subconcussive blows, rather than concussions, may be the underlying cause, identifying this with any certainty faces the same correlative challenges. Second, we cannot rule out a very complex interaction of modifiable and nonmodifiable risk factors, many of which have likely not yet been identified. Finally, primary mood disorder or drug and alcohol abuse may be contributing factors as well.

Equipment

Unfortunately, no protective equipment currently exists to prevent a concussion.[24] Helmets used in alpine sports, equestrian, hockey, and American football are designed to prevent skull fractures, and they are quite adept at accomplishing this.[24] Despite technological improvements, however, no helmet has been shown to prevent concussions. Improving helmet technologies can decrease impact forces, but this has not resulted in decreased incidence of concussions.[24] Additionally, we do not know if helmets assist with decreasing subconcussive blows. In some cases, the use of protective equipment actually results in more aggressive and dangerous playing techniques and may paradoxically increase injury rates.[24]

Mouth guards can prevent dental trauma, but again, they do not prevent concussions.[2,19] Padded headgear in rugby[21,26] and soccer[30,41] also does not prevent concussions or minimize

subconcussive blows. The focus, therefore, must shift to other modifiable factors.

Rule Changes

Rule changes in multiple sports have effectively made sports safer.[24] Examples include moving up the kickoff line in American football, eliminating upper limb-to-head contact during headers in soccer, and setting age limits for body checking in youth hockey.[24] Some sports, such as rugby, may also need rule changes to allow for off-field assessment without penalizing the team.[24]

New and existing rules that are designed to protect the safety of athletes are only as effective as their implementation. Officials are charged with the important task of enforcing rules, and coaches and officials must model good behavior for their athletes. Players must also abide by the rules of fair play and avoid overly aggressive behavior or tactics that are employed with the intention to harm. Proper technique and behavior, limitations on contact practices, and contact restrictions by age group all have the potential to prevent head injury.[15]

Legislation can provide a uniform standard for concussion management and safety, particularly for youth sports.[15] There are 3 tenets to any effective legislation regarding concussion: education of parents, athletes, and coaches; removal from play of any athlete suspected of suffering a concussion; and medically supervised graded return to play. In the 2 years after passage of the Lystedt Law in Washington State, the reported number of concussions in high school athletes increased (Jinguji et al, unpublished data, 2013). This may represent increased awareness of concussions and acknowledgment of their importance. Improved recognition and reporting of concussion symptoms should help to promote prompt removal from play when indicated.

Return to Play

A key component to preventing long-term consequences is appropriate medical care from the injury onset.[15] The newly updated Zurich guidelines[24] continue to provide the most up-to-date management of acute concussion. The key tenets are removal from play with symptom onset and no same-day return to play. Return to play follows a graded process, begins only once asymptomatic, and is managed by a properly trained health care professional. Neuropsychological testing can also assist with timing of return to play. Athletes should be given clear advice about physical and relative mental rest, avoiding alcohol, and expecting a graded return to play. Athletes with symptoms that persist beyond 10 days should be evaluated and managed in a multidisciplinary setting by providers with experience in sports-related concussions.[24] In some cases, prolonged symptoms may represent undiagnosed depression or anxiety rather than continued effects resulting directly from the concussion, highlighting the need for a team approach to care.[25]

A culture shift has already begun in many sports but needs continual reinforcement to be maintained. The goal is to make the era of players showing their physical and mental toughness by ignoring concussions and playing while symptomatic a relic of the past. This culture change is propagated through continued education of athletes, parents, coaches, officials, and the media.

Many former athletes who have been diagnosed postmortem with CTE had continued boxing or playing despite continued neurological symptoms.[22] It is currently unclear whether this may also have increased their risk of developing CTE and whether the current recommendations to rest until symptom resolution may decrease this risk.

COUNSELING ON RISKS

Any discussion regarding CTE with athletes and families must begin with acknowledging that much is unknown. Media reports have been beneficial in raising awareness of concussions, but can also create undue panic when information is sparse. It is important to validate concerns without causing fear.

Chronic traumatic encephalopathy has not been demonstrated to be related to concussions alone or simply exposure to contact sports.[24] The large number of athletes participating in contact sports and the relatively low number of CTE cases indicates that there are likely other factors playing a role.[15] CTE research is still in its infancy, and the number of unknowns makes counseling concerned athletes and parents even more challenging.

Athletes must be informed that the incidence and prevalence of CTE in athletes is currently unknown and will likely remain so until long-term prospective studies have been performed. It is a disease that develops decades after exposure and currently can only be diagnosed at autopsy.

Most importantly, correlation does not equal causality.[25] While there is certainly cause for concern, the available literature does not allow us to identify which of the many possible risk factors contribute to the development of CTE. Proposed factors include total number of concussions, number of subconcussive blows, drug and alcohol use and abuse, medical and psychiatric comorbidities, and genetic risk factors. Chronic inflammation from medical comorbidities that are extremely prevalent in the general population, such as obesity, diabetes, and hypertension, may play a role in the development of CTE.[10] The type, frequency, and amount of trauma needed to induce CTE has not yet been elucidated.[23] Some have questioned whether there is an age threshold.[10] It is unclear whether playing while symptomatic from concussions may also have increased risk in some individuals.

RETIREMENT DECISIONS

The authors' personal experience dictates that some school districts have implemented blanket policies prohibiting student athletes from returning to play after 3 concussions. This type of policy does not acknowledge the complexity of concussion management and retirement decisions. The decision to retire an athlete hinges on much more than simply the number of concussions. There is no predefined number of concussions that is too many[20]; rather, multiple factors come into play. These

include symptom duration and severity of previous concussions and ease of sustaining a subsequent concussion.[4]

Retirement may be considered in an athlete with more than 3 previous concussions with increasing symptom duration, particularly more than 3 months, and lowering of the threshold for sustaining a concussion.[5] Similarly, athletes who have suffered only 1 concussion but were symptomatic for months should also consider retirement.[5]

Athletes with prolonged unresolved postconcussion symptoms, permanent neurologic signs or symptoms, neuropsychological testing that has not returned to baseline, or a report of decreased academic performance should not return to play.[37] Athletes with brain imaging studies that show a lesion that puts the athlete at risk of further injury should also not return to play.[4,5] If advanced imaging becomes more standard practice, unresolved deficits on functional MRI may also require discussion of retirement,[37] though these are currently used only for research purposes and not clinical decision making.

The age of the patient may also influence retirement discussions. Recommendations may be more conservative in the adolescent athlete than in adults.[4] It may be prudent to be more conservative with young individuals who are considering a career that will place them at increased risk of concussion as adults as well.

CONCLUSION

Media coverage has raised the public's awareness of concussion and its potential long-term effects, including CTE. Despite the flood of attention, much still remains unknown. When discussing risks with athletes and families, it is important to recognize both what is known and unknown. Case reports and postmortem histopathological analysis, unfortunately, do not allow us to determine causality or even to identify risk factors and their relative contributions to the development of CTE. The best course of action is to follow the Zurich guidelines[24] for management of acute concussion and to have honest and open dialogue when considering retirement from sport.

It seems prudent to recommend:

1. Removal of all players suspected of sustaining a concussion.[24]
2. No same-day return to play (RTP).[24]
3. No RTP until symptoms have resolved in order to avoid premature RTP.[24]
4. Medically supervised and graded progression through RTP protocol after symptom resolution.[24]
5. Consideration of retirement from contact sports for athletes with prolonged symptoms.[5]
6. Retirement for those with permanent symptoms.[5]

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