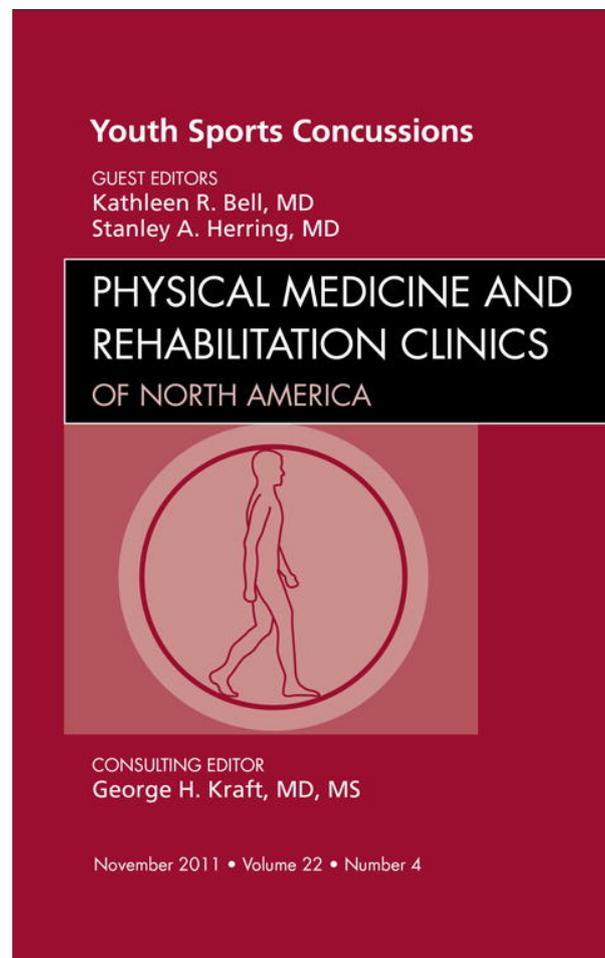


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# Long-Term Consequences: Effects on Normal Development Profile After Concussion

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## KEYWORDS

- Concussion • Development
- Chronic traumatic encephalopathy
- Postconcussion syndrome • Youth

In the United States, approximately 1.7 million people sustain a traumatic brain injury (TBI) annually; these injuries account for 1.365 million emergency room visits and 275,000 hospitalizations each year.<sup>1</sup> The majority of these TBIs are minor, with 75% of these injuries classified as mild TBIs (mTBI) or concussions.<sup>2</sup> These numbers

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may, however, vastly underestimate the total incidence of concussion, as many individuals suffering from mild or moderate TBI do not seek medical advice, especially in the 81% to 92% of cases when the concussion is not accompanied by loss of consciousness.<sup>1,3-5</sup> Beyond the burden of the injury itself, these TBIs have significant direct and indirect economic consequences, estimated at more than \$60 billion annually in the United States alone.<sup>6</sup>

A concussion is a brain injury caused by a force transmitted to the head from a direct or indirect contact with the head, face, neck, or elsewhere, which results either in a collision between the brain and skull or in a strain on the neural tissue and vasculature.<sup>7,8</sup> This impact or strain is believed to cause the symptoms of concussion through a cascade characterized by abrupt neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, altered glucose metabolism and cerebral blood flow, and impaired axonal function.<sup>8</sup> Although these injuries are known to cause short-term deficits, the long-term effects of this neuropathologic cascade are less defined.<sup>9-14</sup>

Clinically the acute signs and symptoms of a concussion are similar in children and adults, and can include physical signs (eg, loss of consciousness, amnesia), behavioral changes (eg, irritability), cognitive impairment (eg, slowed reaction times), sleep disturbances (eg, drowsiness), somatic symptoms (eg, headaches), cognitive symptoms (eg, feeling “in a fog”), and/or emotional symptoms (eg, emotional lability).<sup>15</sup> These deficits are observed in the absence of structural brain damage in diagnostic magnetic resonance imaging (MRI).<sup>16,17</sup> While the vast majority of these symptoms resolve spontaneously, many others may linger.<sup>9</sup> In addition, no two concussions have the same presentation or identical outcomes.<sup>18</sup>

The specific mechanism underlying neural tissue damage, however, appears to be different in the adult versus the developing brain.<sup>19,20</sup> While severe TBI has been shown to have both serious and long-term consequences on personality, mood, and cognition, the precise effect of concussions on development has yet to be fully elucidated.<sup>21-27</sup> Furthermore, immature neural tissue differs from mature tissue in response to injury, in terms of both plasticity and altered developmental trajectory.<sup>28</sup> The structure of the brain, in relation to the skull and its musculature, is also dissimilar in adults and children, leading to different biomechanics and thus different injury profiles.<sup>29,30</sup> As a result, different presentations and outcomes would be expected in response to a concussion experienced in youth as compared with one experienced as an adult.

## LONG-TERM EFFECTS OF POSTCONCUSSION SYNDROME

The symptoms of a concussion may take some time to resolve, resulting in significant long-term burden. When the symptoms of concussion persist as a variety of cognitive, somatic, and behavioral changes, these lingering deficits comprise postconcussion syndrome (PCS).<sup>17,31-33</sup> PCS is defined by the *International Classification of Diseases, 10th Revision* (ICD-10) as the occurrence within 1 month of injury of at least 3 of the 8 symptom categories listed in **Box 1**.<sup>34</sup> The *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revised) (DSM-IV-R) requires the presence of symptoms in at least 3 of 6 categories for at least 3 months after injury in addition to evidence of neuropsychological dysfunction, as outlined in **Box 2**.<sup>35</sup> Whether PCS is experienced following an mTBI seems to be dependent on a combination of factors, including premorbid vulnerability, postinjury psychological adjustment, and postinjury changes in brain function.<sup>36</sup> While most of these symptoms typically resolve within a few days or weeks following mTBI or other head injury, some individuals suffer from PCS for months or longer and, although studies remain conflicting, it is believed

**Box 1****Characteristics of postconcussion syndrome according to the ICD-10**

History of head trauma with loss of consciousness precedes symptom onset by maximum of 4 weeks

*Three or more symptom categories:*

- Headache, dizziness, malaise, fatigue, noise intolerance
- Irritability, depression, anxiety, emotional lability
- Subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment
- Insomnia
- Reduced alcohol intolerance

Preoccupation with above symptoms and fear of brain damage with hypochondriacal concern and adoption of sick role

*Data From World Health Organization.* The ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research. Geneva (Switzerland): World Health Organization; 1993.

that as many as 15% of people with a history of mTBI still suffer from deficits 1 year after injury.<sup>17,37,38</sup>

Adults with PCS often initially present with physical symptoms such as dizziness and headache in the first weeks following injury, with psychosocial symptoms such as depression and irritability first appearing up to a month later.<sup>39</sup> These findings mimic those of rodent models, which have reported both impaired learning and

**Box 2****Characteristics of postconcussion syndrome according to the DSM-IV-R**

A history of head trauma that has caused significant cerebral concussion (eg, with loss of consciousness, posttraumatic amnesia, or seizures)

Neuropsychological evidence of difficulty in attention or memory

*Three or more symptoms that last at least 3 months and have an onset shortly after head trauma or represent substantial worsening of previous symptoms:*

- Fatigue
- Disordered sleep
- Headache
- Dizziness
- Irritability or aggression with little or no provocation
- Anxiety, depression, or affect lability
- Changes in personality
- Apathy or lack of spontaneity

The symptoms result in significant impairment in daily functioning that reflects a decline from previous level

*Data from American Psychiatric Association.* Diagnostic and statistical manual of mental disorders. 4th edition. Washington, DC: American Psychiatric Association; 1994.

depressive-like behavior in mice following mTBI, perhaps mediated by apoptotic cell death.<sup>40–42</sup> In addition, single and repeated concussions in adults have been shown to be correlated with cognitive deficits months following the injury.<sup>43</sup> Executive functioning impairment also appears to persist, with adults who had experienced an mTBI 6 months prior found to have significantly decreased information processing speed.<sup>44</sup> At 1 year after injury, the most common symptoms appear to be a combination of the physical, the psychosocial, and the cognitive, with reports of headaches, dizziness, disturbances of senses, light and noise sensitivity, and various psychiatric symptoms, including depression, anxiety, coping issues, and psychosocial disability.<sup>45,46</sup> In addition, studies have suggested that women are more likely to develop PCS, in terms of both more symptoms reported and a longer duration of impairment.<sup>47</sup>

Some adults continue to show motor deficits, functional deficits, and persistent depressive symptoms more than 1 year after injury.<sup>48–50</sup> The data here are conflicting, however, with other studies indicating that neuropsychological deficits appear to resolve by 1 year after injury. These latter studies tend to include all individuals who had been exposed to any mTBI rather than just those who experienced PCS symptoms; as a result, the sample is overly dilute and the resulting lack of association is not surprising.<sup>51–54</sup>

Of interest, several studies have looked at how beliefs regarding expected outcome in response to brain injury might influence an individual's risk of developing PCS. One study found that individuals who had suffered an mTBI and who indicated that they believed their symptoms would have serious negative consequences on their lives were significantly more likely to experience PCS at 3 months following the injury. In fact, these beliefs regarding the perceived severity at the time of injury were more predictive of PCS symptoms at 3 months than were the total number of PCS symptoms reported immediately following the injury.<sup>45</sup> Another study evaluating attitudes surrounding injury recovery found that self-ratings of PCS symptoms were positively related to emotion-focused coping strategies and negatively related to problem-focused coping in adults who had experienced an mTBI.<sup>55</sup> These findings suggest that one's attitudes can influence the extent to which a concussion has long-term, persistent effects.

Although PCS is considered to be fully recoverable with proper treatment, suffering from PCS-related symptoms for an extended time may delay an individual's return to work, adversely affect one's quality of life, and result in additional social and economic costs.<sup>17,31,45</sup> The deficits caused by these symptoms may also have an indirect long-term effect by exacerbating a preexisting depression or impairing the ability to adequately cope with stress.<sup>56–58</sup> In addition, there is some evidence that concussions result in chronic motor and neuropsychological changes over 3 decades following injury<sup>59</sup>; however, these findings may be attributable to an early-stage neurodegenerative disease associated with concussion, as discussed later.

Although studies and diagnostic criteria of PCS initially reported dissimilar symptoms for adult and pediatric populations, it is now acknowledged that children and young adults report a PCS that is similar to adults and may suffer from the same behavioral, emotional, and somatic difficulties following mTBI.<sup>36,60</sup> Many of these initial studies of youth concussions focused on athletes, as they tend to be at increased risk of experiencing concussions.<sup>5</sup> Although college football athletes report a higher incidence of concussion than high school athletes, it has been reported that high school athletes take longer to recover, based on neuropsychological testing.<sup>61</sup> This finding of increased youth susceptibility to PCS has been extended to other sports and activities, and is perhaps explained by the fact that the frontal lobes do

not fully develop until late adolescence.<sup>43</sup> Rodent models have also suggested that the immature brain is more susceptible than the adult brain to apoptosis following mTBI.<sup>62,63</sup> In fact, one prospective cohort study found that age at the time of injury and extent of extracranial injury were the two strongest independent predictors of functional outcome at 6 months after injury.<sup>64</sup> Even in young adults well enough to enroll and continue in college, there is evidence that PCS symptoms may last for years, and that there may be gender differences in PCS resolution, with women reporting more lingering mood and anxiety symptoms.<sup>65</sup>

Children differ significantly from adults and adolescents not only in size but also biomechanically, pathophysiologically, neurobehaviorally, and developmentally.<sup>28</sup> Because the developing brain is more plastic than the mature brain, younger age at the time of injury was originally thought to have a beneficial effect on recovery and expected outcome.<sup>66</sup> However, current literature indicates that this is not the case; the developing brain appears, in fact, to be more vulnerable to diffuse brain injury. Traumatic injury to the immature brain results in a prolonged period of pathogenesis in both cortical and subcortical structures, leading to progressive neurodegeneration, hyperactivity, and sustained cognitive impairments.<sup>67,68</sup>

Although early studies showed either a small or no effect of head injuries on the developing brain, many of these studies had flawed designs; less than half of the 56 studies reviewed by Satz and colleagues<sup>69,70</sup> from 1970 through 1998 met even 4 of the 6 following recommendations for methodologically sound studies: (1) the inclusion of control groups (either with no injury or with other body injury); (2) the use of a longitudinal design with follow-up assessment post injury; (3) a clear definition of mild injury, without the inclusion of children with more severe injuries; (4) the inclusion of at least 20 children with mTBI; (5) the use of standardized tests to measure outcomes; and (6) controls for preinjury risk factors.

The most methodologically sound studies have found that children report worse cognitive symptoms more than 1 year after concussion than adults. These deficits are first reported months after the original injury and affect the child's school work or abilities to function at home.<sup>71</sup> Children aged 6 to 12 years with mTBI have impaired executive functioning and attention 1 year after injury compared with noninjured controls.<sup>72</sup> An mTBI may also cause linguistic changes that adversely affect Verbal IQ and expressive language. Of note, although these deficiencies improved by 6 months after injury, no additional improvement was observed between 6 and 24 months.<sup>73</sup> In such cases where symptoms persist, PCS may adversely affect a child's conduct and personality, and can lead to extended school absence and limitations on athletic play. In fact, one study reported that children who showed more PCS symptoms displayed worse overall adjustment in comparison with children with fewer PCS symptoms.<sup>36</sup> It has also been suggested that individuals with higher cognitive ability have better outcomes following head injury, because they may be able to recruit alternative and additional neural substrates to compensate for tissue damage.<sup>71,74,75</sup>

Although animal models have elucidated the general pathophysiology responsible for acute concussive symptoms, the underlying cause of sustained PCS remains a matter of debate. However, several pathologic mechanisms have been proposed. Some make the pathophysiologic case that a contributing factor for sustained PCS is the microstructural damage of the brain from head injury. Given that the acute injury causes the aforementioned pathophysiologic cascade, it is not unlikely that some of the resulting microstructural damage can persist in some cases and result in the persisting symptoms of PCS sometimes observed.<sup>31</sup> However, as already mentioned for mTBI in adults, the correlation between increased risk of sustained PCS in children

with negative coping strategies or beliefs about their mTBI symptoms indicates that there may also be a psychopathologic cause to this long-term PCS.<sup>45,55</sup>

This matter is further complicated by various methodologic shortcomings in mTBI and PCS research.<sup>76</sup> These limitations may include retrospective, cross-sectional designs, a lack of appropriate control groups, and a failure to separate different degrees of PCS.<sup>36,39</sup> In addition, studies rely heavily on the self-report of postconcussive symptoms by patients; this has a history of being unreliable, and studies show that a patient's self-report may be the result of simple malingering, an involvement in litigation, or recall biases such as the "good old days" bias, the idea that individuals who sustain an injury often underestimate problems preinjury.<sup>17,77</sup> Finally, whereas PCS is an acknowledged condition, there is a disagreement between ICD-10 and DSM-IV diagnostic criteria; this disagreement emphasizes the confusion over the underlying cause of long-term PCS. Whereas the ICD-10 criteria classifies PCS as symptoms without neuropsychological impairment and focuses instead on premorbid conditions and postinjury psychological adjustment, the DSM-IV criteria do require this neuropsychological impairment and seem to assume that PCS and related symptoms are at least partially caused by an underlying brain trauma.<sup>78</sup> The variability in diagnostic criteria, and the assumptions about PCS that this variation implies, result in different incidence estimates and limited diagnostic agreement when dealing with PCS patients.<sup>79</sup>

The enduring effects of PCS appear to be a combination of the biologic, the physiologic, the psychological, and the social. For both the pediatric and adult population, future research that incorporates genetics, advanced neuroimaging, refined cognitive and postconcussive symptom measures, and social environment research can help to achieve an integrated "biopsychosocial" model that may aid in the management of long-term PCS.<sup>78</sup> This, along with effective education and rehabilitation of patients, will work to reduce the incidence and burden of long-term PCS in TBI patients.

## EFFECTS ON BEHAVIOR

Having sustained a previous concussion may alter a child's long-term developmental trajectory years after the symptoms of PCS subside. Studies of PCS typically only follow children for up to 1 year after injury, potentially before the full effects of the injury have manifested themselves. As a result, these studies are unable to measure the extent of the long-term detrimental effects of an mTBI on the developing brain. To properly evaluate the long-term consequences of youth concussion, studies must examine cognitively mature individuals who previously experienced a concussion in their youth.<sup>80</sup>

Because the prefrontal cortex is one of the last brain structures to mature, it is not surprising that parents report attention deficits, hyperactivity, or conduct disorder following a head injury to their child.<sup>60</sup> In addition, it has been shown that the number of long-term neurobehavioral symptoms in children is related to the severity of the initial mTBI as well as the child's neuropsychological functioning, academic performance, emotional adjustment, and adaptive functioning.<sup>36,81</sup>

The majority of previous studies examining the effects of brain injuries on development years after the injury have focused on more severe injuries.<sup>82–85</sup> However, these studies of moderate and severe TBI suggest a specific window of time during which the brain may be more vulnerable to injury; TBI experienced in middle childhood and later appears to be less detrimental than injuries sustained earlier.<sup>86–91</sup>

One cohort study of 490 children who experienced an mTBI before age 14 years, and who had no prior history of psychiatric illness, found that these children were

significantly more likely to have psychiatric issues in the 3 years following injury than were uninjured controls. The children most commonly presented with attentional problems in the first year following injury. However, there was no difference observed in children who had already had a prior history of psychiatric illness in the year preceding the injury.<sup>92</sup>

These studies are complicated by the fact that the children more likely to experience concussions were also more likely to have undiagnosed psychiatric issues. To circumvent this issue, some studies have used detailed retrospective questionnaires to assess preinjury psychiatric status. One prospective longitudinal study found that children who experienced an mTBI requiring hospitalization before age 10 years displayed increased hyperactivity/inattention and conduct disorder between the ages of 10 and 13 compared with children who had not experienced an mTBI, as rated both by their mothers and their teachers.<sup>89</sup> This cohort has been followed through age 16, and these issues have been shown to persist.<sup>93</sup> However, these children did not display any deficits in intelligence or academic skills. In addition, children whose injuries did not require hospitalization showed no differences from control children without a history of mTBI. Although there were differences observed in hyperactivity/inattention and conduct disorder based on age at the time of injury (those injured between 0 and 5 years old and those injured between 5 and 10 years old), these differences were not statistically significant.<sup>89</sup> A later study confirmed these findings and also reported that children injured in preschool had progressively worsening parent and teacher ratings of hyperactivity/inattention and conduct disorder when followed longitudinally from age 7 to 13 years.<sup>80</sup> Another study of 45 adults, with an average age at injury of 8.9 years (standard deviation of 3.3), found that those who experienced posttraumatic amnesia for at least 30 minutes had statistically significant decreases in measures of attention and memory more than 2 decades later.<sup>94</sup> These attentional findings are not surprising, as the prefrontal cortex does not fully develop until late adolescence. In addition, these deficits were not observed in individuals injured as adults.<sup>95</sup>

The effects of mTBI on children do not always end with the resolution of PCS, but may have long-term effects on cognitive processing, mood, and behavior. These delayed behavioral impairments suggest the need for continued monitoring and intervention in children, even years after initial concussion.

## WHEN TO RETIRE AFTER A CONCUSSION

Following a concussion, the absolute contraindications to return to a contact/collision practice or competition sport include:

1. Abnormal neurologic assessment
2. Symptomatic of postconcussion signs/symptoms at rest or exertion
3. If done, neuropsychological battery not baseline or above
4. If done, head computed tomography or MRI shows a lesion placing the athlete at increased risk of head injury (edema, hemorrhage, hydrocephalus, cavum septum pellucidum, arachnoid cyst).

The relative contraindications to return to collision practice or competition include:

1. Postconcussion symptoms that last many months and not days
2. Mild or indirect blows (whiplash) that produce significant and lengthy postconcussion symptoms.

Thus there are absolute and relative indicators for retirement. Neither are based on a particular number of concussions, but rather on the athlete's response, including

duration of symptoms and ease of being concussed. Keeping in mind the increased vulnerability of the developing brain, it is suggested that one might be even more conservative in the under-18 age group as compared with adults.<sup>96</sup>

## **DEGENERATIVE DISEASE**

Brain trauma has long been thought to play a role in initiating or accelerating the molecular cascade involved in several degenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS).<sup>97–99</sup> In addition, repetitive concussive and subconcussive brain trauma has been implicated as the primary risk factor for developing the progressive neurodegenerative disease chronic traumatic encephalopathy (CTE), as well as the motor neuron disease variant chronic traumatic encephalomyelopathy (CTE-M).<sup>100,101</sup>

### ***Alzheimer Disease***

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Several epidemiologic studies have found a relationship between head trauma and AD in later life.<sup>102–108</sup> However, all of these studies based their analyses on a clinical diagnosis of possible or probable AD. Without neuropathologic confirmation of disease, it is possible that other neurodegenerative diseases, such as CTE, were in fact partially or fully responsible for the observed clinical dementia.<sup>109</sup> However, one retrospective study found that individuals with a history of TBI had a higher than expected prevalence of AD pathology observed at autopsy.<sup>110</sup> This result could in part be explained by the fact that  $\beta$ -amyloid precursor protein (APP) is shown to temporarily accumulate in response to acute TBI in genetically susceptible mice; the cleavage of APP results in the  $\beta$ -amyloid ( $A\beta$ ) characteristic of AD.<sup>111,112</sup> More research is certainly needed, both to elucidate the relationship between AD and mTBI, and to disambiguate potential cases of CTE from clinically diagnosed cases of probable and possible AD.

### ***Parkinson Disease***

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TBI has also been implicated as a risk factor for PD.<sup>98,113</sup> Although the nature of the relationship is poorly understood, animal models suggest that TBI results in  $\alpha$ -synuclein deposition, a protein shown to be the primary building block of the Lewy bodies in PD.<sup>112,114,115</sup> However, neither animal models nor human studies have conclusively shown a relationship between concussions and the development of PD.

### ***Chronic Traumatic Encephalopathy***

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CTE is a progressive neurodegenerative tauopathy caused by repeated concussive and subconcussive impacts. Because repeated impacts are thought to be necessary to initiate the disease process, CTE is typically found in those at high risk for experiencing repetitive head trauma, including athletes, those with exposure to injury due to military service or occupation, and individuals who exhibit seizures and/or head-banging behavior.<sup>100,109</sup> In fact, CTE was initially named dementia pugilistica because of its association with the repetitive head trauma experienced by boxers in the ring.

However, head trauma alone is not sufficient to initiate the neuropathologic cascade of CTE. There are many potential risk factors that likely play a role in determining which individuals develop CTE and which individuals do not, given similar head trauma histories. There is some evidence that the ApoE E4 allele may be associated with CTE development.<sup>100,101</sup> In addition, the relationship between the development of CTE and the number or severity of head injuries is not yet clear, as some athletes diagnosed with CTE had no reported concussion history despite a history of repetitive subconcussive head trauma.<sup>100,101</sup> In addition, the age at which an individual begins

experiencing head injury and the time interval between concussions may play a role in the development of CTE.

Although the disease process likely starts at the time of injury, the initial signs of CTE do not typically manifest until decades later. Therefore, the time course for the presentation of CTE symptoms distinguish it from the cumulative effects of multiple injuries or a form of prolonged PCS. CTE can only be diagnosed post mortem at this time, and as such the precise clinical presentation and the cascade of events preceding it are not yet known.<sup>116</sup> In addition, because the diagnosis of CTE relies on postmortem tissue analysis, the precise epidemiology of CTE is not yet known. Although the majority of professional and collegiate athletes examined for CTE have in fact been found to have had the disease, this represents a biased sample in that families who suspect their loved ones may be impaired are more likely to agree to brain donation for research purposes.

However, CTE is believed to be characterized clinically by a progressive decline of memory and executive functioning; mood and behavioral disturbances that include depression, apathy, impulsivity, anger, irritability, suicidal behavior, and aggressiveness; gait changes that resemble Parkinsonism; and, eventually, progression to dementia. Once this disease process is initiated, the neurodegeneration typically progresses slowly, with a mean survival duration of 18 years following the onset of symptoms.<sup>100,117–119</sup>

CTE is characterized neuropathologically by a distinctive pattern of extensive tau-immunoreactive inclusions scattered throughout the cerebral cortex in a patchy, superficial distribution, with focal epicenters at the depths of sulci and around the cerebral vasculature; extensive tau-immunoreactive inclusions in limbic and paralimbic regions as well as brainstem nuclei; and a relative absence of A $\beta$  deposits. On gross examination, CTE is characterized by generalized atrophy and enlarged ventricles, specific atrophy of the frontal and medial temporal lobes, degenerations of white matter fiber bundles, cavum septum pellucidum often with fenestrations, thinning of the hypothalamic floor, and shrinkage of the mammillary bodies.<sup>100</sup>

Although CTE may have similarities with AD, they are two quite distinct diseases. Clinically, CTE typically presents with age of onset in the 40s and 50s as opposed to onset after age 65 years in sporadic AD. In addition, the clinical progression of disease is much slower, often lasting decades, and is characterized by a subtle deterioration in personality and behavior.<sup>100</sup> Neuropathologically both diseases share tau immunoreactivity, but the widespread distribution of neurofibrillary and glial tangles in the frontal, insular, and temporal cortices, white matter, diencephalon, brainstem, and spinal cord is considerably more extensive in CTE than in AD. Furthermore, the pattern of the neurofibrillary abnormalities is entirely distinct from AD or any other tauopathy, especially when considering the absence of the neuritic A $\beta$  deposits characteristic of AD.<sup>100,120</sup> However, additional research is needed to better understand the mechanism underlying these changes.

### **Motor Neuron Disease**

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Although genetic mutations have been identified that cause ALS, 90% to 95% of ALS cases are sporadic.<sup>121,122</sup> Many risk factors have been identified as possibly contributing to these sporadic cases, but trauma specifically has been implicated as a risk factor that may initiate the molecular cascades resulting in ALS.<sup>99,123</sup> In one case-control study, researchers found that injuries that had occurred in the previous 10 years had the strongest association with diagnosis of ALS.<sup>99</sup> Another case-control study also found that the risk of ALS increased when the last head injury occurred closer to the time of diagnosis.<sup>124</sup> However, other studies have disputed this

association.<sup>125</sup> On the whole, these findings suggest that head injury may play a role in triggering the onset of motor neuron disease.

Motor neurons in sporadic ALS are often found with TDP-43-immunoreactive inclusion bodies that appear either as rounded hyaline inclusions or as skein-like inclusions; as a result, TDP-43 has been implicated in the pathogenesis of motor neuron disease.<sup>126,127</sup> Widespread TDP-43-positive inclusions have also been found in the vast majority of cases of CTE, and are typically found in the brainstem, basal ganglia, diencephalon, medial temporal lobe, frontal, temporal, and insular cortices, and subcortical white matter. A subset of individuals with CTE also develops a progressive motor neuron disease characterized by profound weakness, atrophy, spasticity, and fasciculations. In these individuals, both tau neurofibrillary pathology and extensive TDP-43-immunoreactive inclusions and neurites were found in the motor cortex of the brain and in the spinal cord in a distribution not characteristic of sporadic ALS.<sup>101</sup> Although these initial findings merit further investigation, the co-occurrence of widespread TDP-43 and tau proteinopathies in CTE suggests that repetitive head injury might be associated with the deposition of two abnormally phosphorylated, misfolded proteins, and that in some individuals the TDP-43 proteinopathy is associated with the development of a motor neuron disease.

## IMPLICATIONS ON ATHLETIC PARTICIPATION

As a result of these potential long-term consequences, both the incidence and the severity of youth concussion must be reduced. There are several approaches worth evaluating toward this end.

One potential solution involves the development and introduction of better equipment (eg, helmets and mouth guards) that are specifically designed to attenuate the forces associated with concussions. However, although helmets have been shown to decrease the incidence of facial injury as well as moderate and severe TBI, and mouth guards help protect against dental and orofacial injury, there has been no evidence to date that the newest equipment reduces the incidence of concussions or severity of concussion symptoms.<sup>5</sup>

In addition, when new equipment requirements are introduced into a sport, athletes' behavior often changes, resulting in a riskier style of play reflecting their increased feeling of protection.<sup>128</sup> In some cases, this has been associated with a paradoxical increase in concussion incidence within an activity.<sup>129</sup>

A potentially more fruitful approach would be to limit an athlete's exposure to the impacts that might result in concussion. This goal could be accomplished through several means, such as decreasing the number of contact practices an athlete participates in each week; practice alone is responsible for up to 1500 impacts of 10 g or more for some football players.<sup>130</sup> Ivy League colleges have taken the lead and recently began implementing this policy, and it is hoped that others will follow suit. In addition, sport-specific rule changes might help reduce the frequency of unnecessary and dangerous collisions, thereby decreasing the burden of athletic concussion.

In most instances, when concussions are properly treated they are not believed to be associated with any long-term sequelae. Ensuring that individuals receive proper medical care, and are given adequate physical and mental rest during recovery, should ensure that these injuries fully heal. Adopting uniform return-to-play guidelines, such as those already discussed here, would help ensure athletes are not permitted to play too soon.

Along these lines, proper education of athletes, coaches, medical professionals, and the general public is necessary to identify and properly treat concussions. There

are many organizations, such as the Centers for Disease Control and Prevention, the Brain Injury Association, and the Sports Legacy Institute, working to improve concussion awareness and educational outreach.

## SUMMARY

While most concussions fully resolve within weeks of the injury, for some these concussions can have serious, long-term effects. Concussed individuals can sometimes experience prolonged PCS, lasting for months or even years, which can result in significant physical, emotional, and cognitive stress. In addition, in children and young adults, months of PCS can adversely affect one's developmental trajectory by keeping students out of class and straining personal relationships. In adults, suffering from PCS for an extended period of time may delay one's ability to return to work, resulting in an additional financial and social burden on the concussed individual.

Once the symptoms of concussion subside, in some cases a prior concussion may also have a lasting effect on behavior. These issues are more common in children, as those who have been concussed are more likely to have symptoms of mood or conduct disorders reported by parents and teachers years after injury. Although these findings may in part be due to undiagnosed mood or conduct disorders in children, which resulted in an original injury, the fact that the prefrontal cortex has not fully developed in these injured children provides an additional explanation of aberrant behavior.

In addition, concussions and subconcussive impacts have been shown to increase the risk of developing degenerative disease, sometimes even decades after the injury. There is a good deal of epidemiologic evidence linking a history of head injury with the development of AD, supported by evidence from animal models in response to acute head injury, but additional work is necessary to separate clinically diagnosed AD from other dementias. TBI has also been linked to PD through transient increases in  $\alpha$ -synuclein resulting in an increase in the formation of Lewy bodies. However, the strongest evidence for a direct link between repetitive concussive and subconcussive injury and neurodegenerative disease later in life comes from the study of CTE. Originally found in boxers, CTE has been diagnosed in a wide variety of individuals, all of whom had been exposed to repetitive head injury, be it through participation in athletics, military service, occupational hazards, or some other cause. While the tau diagnostic of CTE may begin to aggregate and form inclusions as early as in the second decade, the first clinical signs of CTE are not typically observed until one's 30s or 40s. CTE presents with cognitive deficits, depression, and behavioral disinhibition, and eventually progresses to full-blown dementia.

Although concussions were once considered relatively benign, mounting evidence indicates that concussions can have long-term consequences, sometimes for years or even decades after the injury. Improved understanding of the risks associated with concussions, and their potentially debilitating consequences, highlights the need for better diagnosis, treatment, and prevention.

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