# The clinical spectrum of sport-related traumatic brain injury

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**Abstract** | Acute and chronic sports-related traumatic brain injuries (TBIs) are a substantial public health concern. Various types of acute TBI can occur in sport, but detection and management of cerebral concussion is of greatest importance as mismanagement of this syndrome can lead to persistent or chronic postconcussion syndrome (CPCS) or diffuse cerebral swelling. Chronic TBI encompasses a spectrum of disorders that are associated with long-term consequences of brain injury, including chronic traumatic encephalopathy (CTE), dementia pugilistica, post-traumatic parkinsonism, post-traumatic dementia and CPCS. CTE is the prototype of chronic TBI, but can only be definitively diagnosed at autopsy as no reliable biomarkers of this disorder are available. Whether CTE shares neuropathological features with CPCS is unknown. Evidence suggests that participation in contact–collision sports may increase the risk of neurodegenerative disorders such as Alzheimer disease, but the data are conflicting. In this Review, the spectrum of acute and chronic sport-related TBI is discussed, highlighting how examination of athletes involved in high-impact sports has advanced our understanding of pathology of brain injury and enabled improvements in detection and diagnosis of sport-related TBI.

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## Introduction

Sport-related traumatic brain injury (TBI) is an important public health concern and is often labelled as a 'silent epidemic'. Estimates suggest that 1.6–3.8 million sport-related TBIs occur annually in the USA alone, and this number includes injuries for which no medical care is sought.[1] This estimate is likely to be conservative, however, given that many sport-related TBIs are unrecognized and unreported. Sports that are associated with an increased risk of TBI include those involving contact and/or collisions, such as boxing, American football, ice hockey, soccer, rugby and the martial arts, as well as high-velocity sports such as cycling, motor racing, equestrian sports, rodeo, skiing and roller skating. Although most sport-related TBIs occur during participation in contact–collision sports and high-velocity sports, participation in any sport carries a risk of experiencing a brain injury.

TBI can generally be classified as acute or chronic. Acute TBI is used to describe injuries that occur immediately at the time of impact, with subsequent signs and symptoms of TBI, whereas chronic TBI refers to the long-term consequences of single or multiple brain traumas. In this Review, the spectrum of acute and chronic sport-related TBI is highlighted, with particular focus on cerebral concussion, diffuse cerebral swelling (DCS, also known as second-impact syndrome), chronic traumatic encephalopathy (CTE) and chronic postconcussion syndrome (CPCS). Improved recognition of concussion through education and proper medical surveillance is of paramount importance for prevention of long-term neurodegenerative disorders in athletes who experience TBI.

## Acute traumatic brain injury

For athletes involved in high-risk sports, there exists a spectrum of acute TBI pathologies that can occur (Box 1). Moderate and severe injuries such as focal brain injuries, diffuse axonal injury, skull fractures and penetrating brain injury are extremely rare in sports, but can, nonetheless, be encountered. A detailed discussion of these severe TBIs is beyond the scope of this Review, but such injuries must always be considered when managing an athlete with acute brain trauma. The most common and challenging acute brain injuries in athletes—namely, cerebral concussion and DCS—are described below.

### Concussion

Concussion is defined as a complex pathophysiological process that affects the brain and is induced by traumatic biomechanical forces.[2–4] A concussion typically occurs following transmission of direct or indirect impulsive forces to the head, which results in rapid onset of short-lived neurological impairments,[2–4] and presents clinically with cognitive, physical and behavioural signs and symptoms (Box 2). The most frequent clinical symptoms include headache, dizziness and memory impairment. Notably, loss of consciousness is not a requirement for diagnosis of concussion. In adults, most concussions

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**Key points**

- In high-impact sports, cerebral concussion is the most common form of acute traumatic brain injury (TBI), but other moderate and severe TBIs can occur
- Cerebral concussion is a clinical diagnosis that can present with cognitive, physical and/or behavioural signs and symptoms, and does not require loss of consciousness
- Second-impact syndrome is a rare and controversial syndrome that must be considered in the management of a young athlete with concussion
- Increased exposure to sport and advancing age are putative risk factors for the development of chronic traumatic encephalopathy (CTE)
- Antemortem diagnosis of CTE is difficult, and further research is needed to establish effective biomarkers that reflect disease activity
- Chronic postconcussion syndrome is a form of chronic TBI that is clinically distinct from CTE; neuropathological overlap between these two conditions is unknown

**Box 1** | Classification of acute TBI

Diffuse brain injury
- Cerebral concussion
- Diffuse axonal injury
- Diffuse cerebral swelling

Focal brain injury
- Epidural haematoma
- Subdural haematoma
- Cerebral contusion
- Intracerebral haemorrhage
- Subarachnoid haemorrhage
- Intraventricular haemorrhage
- Subdural hygroma

Skull fracture

Penetrating brain injury

Abbreviation: TBI, traumatic brain injury.

tend to resolve spontaneously within 7–10 days;[5–9] in children and young adolescents, however, the recovery period can be longer.[3] Rather than presenting with structural injury that can be detected using conventional structural neuroimaging, the clinical symptomatology of concussion largely reflects a functional disturbance.[2–4]

*Mechanisms of injury*

Rapid acceleration and deceleration of the brain, including rotational (angular) acceleration, linear (translational) acceleration and impact deceleration, are the primary mechanism by which concussion occurs (Figure 1). Rotational acceleration occurs when biomechanical forces cause the head to rotate, potentially causing axons to stretch and tear, inducing concussion and traumatic axonal injury. Linear acceleration results from biomechanical forces that cause the head to move in the anterior–posterior direction, and is capable of producing gliding contusions in the parasagittal regions of the cerebral cortex and axonal injury in the brainstem.[10] Impact deceleration occurs when the head rapidly decelerates, typically when the head strikes a playing mat or field, or an arena floor (Figure 1c). The impact can lead to coup injury (an injury on the side of the head where the impact was made) and contrecoup injury of the cerebral cortex.[10] Theoretically, impact deceleration can also occur when an athlete's head rapidly decelerates when striking the body of an opposing player (Figure 1d) or fixed structures such as a goalpost, railing, tree or hockey board.

Head impact telemetry (HIT) systems, which are used to measure biomechanical forces transmitted to the brain,[11] have failed to identify an 'impact threshold' for induction of concussion. Video analysis of concussions sustained by professional National Football League players indicates that the majority of blows occur to the side of the helmet and/or facemask.[12] In nonprofessional football players, however, HIT technology reveals that most concussions result from blows to the top of the helmet.[11] Biomechanical forces that are capable of causing brain injury are probably a combination of rotational, linear and/or impact decelerations.

From the point at which biomechanical forces are transmitted to the brain, multiple neuropathophysiological cascades are triggered. The initial neurometabolic cascade involves neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, changes in glucose metabolism and cerebral blood flow, and impaired axonal function.[13] Additional cascades or processes may then initiate or result, including apoptosis, calpain–caspase activation, mitochondrial dysfunction, free radical formation, neuroinflammation, growth factor alterations, and inflammatory processes.[14] Furthermore, an amyloid cascade, either with or without proper clearance of amyloid components, may be initiated.[15]

*Detection and diagnosis*

No devices that enable clinical diagnosis of concussion currently exist. Several neurodiagnostic investigations that may assist in the physician in these cases are, however, available. Neuropsychological testing can aid in determination of the occurrence and resolution of cognitive impairment, but results of these tests should not be used as the sole basis for the decision to allow an athlete to return to play.[3] Standard structural neuroimaging outcomes are typically normal in patients who are evaluated for a sport-related concussion,[2–4] but new structural, functional and/or metabolic imaging technologies may be useful for detection of subtle structural or functional brain injury. For example, gradient-echo MRI sequences in one athlete with a head injury revealed evidence of microhaemorrhages—a finding that is consistent with a shear injury.[16]

Whether diffusion tensor imaging (DTI) is beneficial in evaluation of acute concussion remains to be determined, as studies using this methodology report variable outcomes and findings. In one study published in 2012,[17] researchers observed decreased fractional anisotropy—which is suggestive of decreased fibre-tract integrity—in one of 11 tracts in professional American football players with concussion, but found no abnormalities on susceptibility-weighted imaging (SWI),which would be indicative of prior microhaemorrhages. A 2011 study[18] found increased mean diffusivity (suggestive of axonal injury) in several white matter tracts in the left hemisphere of concussed athletes, but no differences in fractional anisotropy between concussed athletes

and controls. Similarly, no differences were observed in fractional anisotropy in children with concussion compared with controls.[19] By contrast, a case study of a concussed athlete[20] reported significant and colocalized changes in fractional anisotropy and mean diffusivity voxels in the right corona radiata and right inferior longitudinal fasciculus.

Functional MRI (fMRI) has revealed altered activation patterns in athletes with concussion compared with controls. During a finger-sequencing task, concussed players exhibited marked within-subject increases in the amplitude and extent of blood oxygen level-dependent activity (indicative of high levels of brain activity) that localized primarily to the parietal, lateral frontal and cerebellar regions.[21] Concussed athletes also showed altered activation patterns on fMRI compared with controls, even when the athletes performed as well as the controls on the given task.[22] Furthermore, athletes who exhibited hyperactivation on fMRI demonstrated a prolonged clinical recovery.[23]

Magnetic resonance spectroscopy is a noninvasive technique that can be used to identify neurometabolic changes in the acute postconcussion phase.[24–27] Concussed athletes had decreased levels of glutamate (a principle excitatory neurotransmitter) in the primary motor cortex (M1) and decreased levels of *N*-acetylaspartate (NAA)—a marker of neuronal integrity—in the prefrontal and M1 cortices.[24] Such metabolic changes in M1 correlated directly with severity of self-reported symptoms. In a follow-up study, the investigators confirmed their previous findings and also noted that glutamate levels recovered in the chronic postconcussion phase.[25] Other researchers also observed a decrease in NAA levels relative to creatine levels in concussed athletes, but noted that the deficit completely recovered by day 30 postinjury.[26,27] Of interest, athletes who experienced a second concussion during the recovery period were found to exhibit a further decrease in the NAA:creatine ratio and, therefore, the existence of a temporal window of metabolic brain vulnerability to further injury was postulated.[26]

### *Management*

Appropriate management of concussion requires the immediate removal of a player from competition and their evaluation by a health-care professional.[2–4] A subsequent period of cognitive and physical rest, until the athlete becomes asymptomatic, is recommended. Once an athlete is asymptomatic and no longer receiving medications to treat or modify the symptoms of concussion, a gradual stepwise return to competition should be implemented.[3] Medications used in the treatment of concussive symptoms include: analgesics, nonsteriodal anti-inflammatories, antidepressants, anticonvulsants, beta-blockers and triptans for headache; vestibular suppressants and benzodiazepines for dizziness; neurostimulants for fatigue; antiemtics for nausea; and/or medications for depression and anxiety.[28] Neurostimulants, selective serotonin reuptake inhibitors, and anticholinesterase inhibitors have also been used in an attempt to improve neurocognitive performance following TBI.[28–30]

**Box 2** | Symptoms of acute concussion

**Cognitive features**
- Decreased speed of information processing
- Disorientation
- Lack of awareness
- Confusion
- Amnesia or other memory impairments
- Impaired concentration
- Loss of consciousness
- Feeling in a 'fog'

**Behavioural features**
- Sleep disturbance
- Irritability
- Emotional lability
- Nervousness and/or anxiety
- Psychomotor retardation
- Apathy
- Fatigue
- Easily distracted

**Physical features**
- Headache
- Dizziness and/or vertigo
- Nausea
- Vacant stare
- Impaired playing ability
- Gait unsteadiness and/or loss of balance
- Impaired coordination
- Diplopia and/or blurred vision
- Photophobia
- Hyperacusis
- Concussive convulsion and/or impact seizure

When the athlete is asymptomatic at rest and on exertion, he or she can return to full activity.[2–4] For athletes who do not show improvement after cognitive and physical rest for a period of time (for example, 1 month), a low-level, subsymptom threshold rehabilitation and/or exercise programme may be of benefit in improving postconcussion syndrome (PCS).[31,32] The mismanagement of a concussion can potentially result in a persistent PCS and/or second-impact syndrome.[33]

## Diffuse cerebral swelling

DCS is the pathological substrate of second-impact syndrome, and represents a rare but potentially fatal injury that can occur in athletes who sustain a second brain trauma while still symptomatic from a previous concussion. This second-hit trauma leads to a catastrophic neurophysiological response of diffuse brain swelling, cerebral oedema and brain herniation.[34] Second-impact syndrome is thought to arise following loss of autoregulation of cerebral blood flow, which results in vascular engorgement and subsequent increased intracranial pressure and eventual herniation.[34]

Although considered to be a rare phenomenon, the exact frequency of second-impact syndrome is unknown. One study in the USA, however, reported 17 cases among young adults aged 21 years or younger over a 30-year period.[35] Second-impact syndrome has been reported

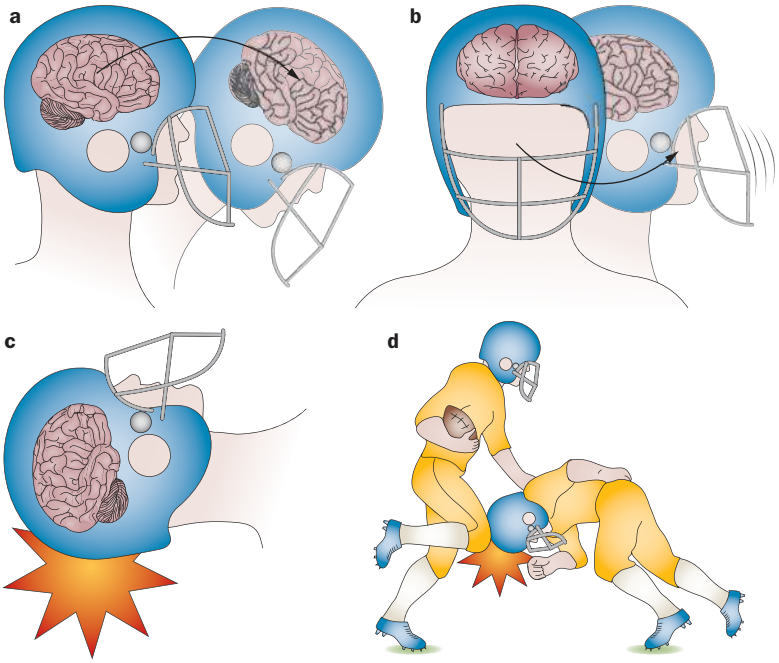


**Figure 1** | Mechanisms of brain acceleration–deceleration secondary to biomechanical forces transmitted to the brain. **a** | Linear (translational) acceleration. **b** | Rotational (angular) acceleration. **c** | Impact deceleration. **d** | Impact deceleration secondary to the head striking an opposing player's body. Permission obtained from Innovative CEUs, LLC ©.

in the context of American football, boxing and ice hockey,[34,36] but its existence has been questioned. One hypothesis is that second-impact syndrome is primary DCS in response to trauma without a pre-existing injury.[36,37] Although rare, DCS remains a major concern in the management of acute concussion in young athletes, owing to the high mortality rate associated with this syndrome.

According to McCrory and Berkovic,[38] the following clinical criteria must be fulfilled for a definitive diagnosis of second-impact syndrome: medical review after a witnessed first impact; documentation of ongoing symptoms following the first impact up to the time of second impact; witnessed second head impact with subsequent rapid cerebral deterioration; and neuropathological or neuroimaging evidence of cerebral swelling without marked intracranial haematoma or other cause of oedema.

## Chronic traumatic brain injury

Chronic TBI encompasses a spectrum of disorders that are associated with long-term consequences of brain injury. The prototype of chronic TBI is CTE—a syndrome that results from long-term neurological damage following repetitive mild TBIs. Dementia pugilistica is the boxing manifestation of CTE, but this diagnosis is typically reserved for cases in which severe dementia develops following a long boxing career. Post-traumatic parkinsonism describes a parkinsonian syndrome that occurs secondary to TBI. This form of chronic TBI includes puglistic parkinsonism—a subtype of dementia pugulistica in which rigidity and tremor predominate, and which can be identified pathologically by the abundance of neurofibrillary tangles in the absence of Lewy bodies.[39] Whereas CPCS is the diagnosis given to athletes in whom postconcussive symptoms do not seem to resolve, a diagnosis of post-traumatic dementia is applied to cases that meet the clinical criteria for dementia after a single moderate or severe TBI. Post-traumatic dementia differs from CTE in that the brain injury is not repetitive but results from a single trauma that is more severe than a concussion.

Evidence suggests that participation in contact sports can increase an individual's risk of neurodegenerative disorders such as mild cognitive impairment, Alzheimer disease (AD), motor neuron disease (MND) or Parkinson disease. This association represents an additional public health concern to the issue of sport-related CTE. A survey of retired professional American football players showed an association between recurrent concussion, clinically diagnosed mild cognitive impairment and self-reported memory problems.[40] Another survey in a similar population of retired athletes revealed a significant, direct association between rate of self-reported concussion and complaints of memory changes, confusion, speech difficulties, problems remembering short lists, and difficulty recalling recent events.[41] In addition, those with a history of self-reported concussion exhibited a high frequency of headache, paraesthesias and vestibular problems that were reminiscent of a CPCS. Higher AD-associated and MND-associated mortality rates were reported in retired professional American football players than in the general US population.

In contrast to the above results, however, two studies failed to identify an increased risk of neurodegeneration among participants of contact–collision sports. Comparison of a cohort of low-exposure (that is, high-school level) American football players to nonplaying individuals found no difference in the risk of dementia, Parkinson disease or MND.[42] In a case–control study of individuals with AD, no association was found between risk of disease and participation in contact sports,[43] although this study was limited by a small sample size. Further investigation is warranted to understand the pathophysiology of chronic TBI and risk of neurodegeneration secondary to repetitive brain trauma.

### Chronic traumatic encephalopathy

CTE is the long-term neurological consequence of repetitive mild TBI. The exact frequency of CTE in modern day sports is unknown but, in 1969, a landmark study of retired boxers from the UK reported a CTE prevalence of 17%.[44] In boxing, longer duration of exposure to sport (measured as the number of bouts), older age at retirement from boxing, and longer length of boxing career, are important variables that can increase an individual's risk of developing CTE.[44]

In a subset of American football players with autopsy-confirmed CTE, a positive correlation was noted between the severity of CTE, exposure to sport, years since retirement, and age at death.[45] Family-reported number of concussions, years of education, lifetime steroid use

and position played, however, were not significantly correlated with the stage of CTE. Repetitive concussion and subconcussion has been linked to the development of CTE,[46] but a threshold of injury (that is, the number of injuries required to cause CTE) has not been established. Interestingly, the proportion of football players with CTE who were carriers of at least one apolipoprotein E (*APOE*) ε4 allele—an allele associated with increased risk of AD—was not significantly different from the proportion of *APOE* ε4 carriers in the general population. Other studies, however, suggest an association between the *APOE* ε4 allele and chronic TBI.[47,48]

### *Clinical presentation*

Clinically, CTE can present with behavioural, cognitive and/or motor-related symptoms (Box 3).[44,45,49–54] Behavioural disturbances are often the earliest findings in CTE and can include depression, mood swings, apathy, impulsivity, aggression and suicidality. With regard to cognitive impairments, athletes can exhibit impaired attention and/or concentration, memory problems, executive dysfunction and, as the disease progresses, the individual may develop dementia. The motor manifestations of CTE—such as spasticity, tremor (parkinsonian type), ataxia, dysarthria and problems with coordination—reflect injury to the pyramidal tracts, the extrapyramidal system and the cerebellum.

MND has been noted in a subset of athletes with CTE,[45,50] but whether this phenotype represents a unique subtype of CTE or an overlap of two distinct disease processes, which may or may not be associated with repetitive brain injury and/or a common genetic predisposition, remains unclear. In a subset of CTE cases, headache also seems to be a prominent feature.[45] Again, whether these cases represent comorbid CPCS (discussed below) or a distinct clinical phenotype of CTE has yet to be determined.

### *Pathological classification*

The pathological features of CTE have been well-described and include diffuse brain atrophy, ventricular dilatation, cavum septum pellucidum with or without fenestrations, cerebellar scarring, and depigmentation and degeneration of the substantia nigra.[45,49–51,54,55] As the disease progresses, marked atrophy of the medial temporal lobe, thalamus, hypothalamus and mammillary bodies becomes evident.

Currently, two histopathological classifications of CTE exist.[45,51] Omalu and colleagues have identified four phenotypes of CTE (Box 4),[51] whereas McKee and colleagues have classified CTE into four stages (Box 5).[45] According to the classification scheme of McKee *et al.*, CTE begins focally, usually perivascularly at the depth of the sulci in the frontal cerebral cortex, and involves the superficial layers of the cerebral cortex. The pathology spreads slowly (over decades) to involve widespread regions of the medial cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem and spinal cord. Stages I and II are considered to be mild pathologies and are characterized by neurofibrillary tangles in focal epicenters of the frontal cortices. Stages III and IV represent severe forms of CTE, with more-widespread tau involvement. Notably, all seven cases of AD-associated CTE that were indentified in this study were stage IV, and no pure cases of AD existed in the cohort.[45]

**Box 3** | Clinical presentations of CTE

**Behavioural and psychiatric features**
- Aggression and/or agitation
- Apathy
- Impulsivity
- Depression
- Delusions (such as paranoia)
- Suicidality

**Cognitive features**
- Impaired attention and concentration
- Memory problems
- Executive dysfunction
- Dementia
- Visuospatial difficulties
- Language impairment

**Motor features**
- Dysarthria, including scanning speech
- Spasticity
- Ataxia, including incoordination
- Parkinsonism, including tremors
- Gait disturbance
- Motor neuron disease (possibly)

Abbreviation: CTE, chronic traumatic encephalopathy.

**Box 4** | Omalu neuropathological classification of CTE[51]

**Phenotype I**
Sparse to frequent NFTs and neuritic threads in the cerebral cortex and brainstem but without involvement of the subcortical nuclei (basal ganglia) and cerebellum. No diffuse amyloid plaques in the cerebral cortex.

**Phenotype II**
Sparse to frequent NFTs and neuritic threads in the cerebral cortex and brainstem with or without such pathology in the subcortical nuclei (basal ganglia) and cerebellum. Diffuse amyloid plaques in the cerebral cortex.

**Phenotype III**
Brainstem predominant: moderate to frequent NFTs and neuritic threads in the brainstem nuclei, absent or sparse NFTs and neuritic threads in the cerebral cortex, subcortical nuclei (basal ganglia) and cerebellum. No diffuse amyloid plaques in the cerebral cortex.

**Phenotype IV**
Incipient: absent or sparse NFTs and neuritic threads in the cerebral cortex, brainstem and subcortical nuclei (basal ganglia). No cerebellar involvement. No diffuse amyloid plaques in the cerebral cortex.

Abbreviations: CTE, chronic traumatic encephalopathy; NFT, neurofibrillary tangle.

### *Diagnosis*

A diagnosis of CTE can be definitively ascertained only at autopsy. Clinical diagnosis of CTE can be problematic as the development of chronic neurological sequelae is not temporally related to a single concussive event and the symptoms typically manifest in later life after a

**Box 5** | McKee neuropathological classification of CTE[45]

**Stage I**
Normal brain weight. Focal epicenters of perivascular p-tau, and neurofibrillary and astrocytic tangles involving the sulcal depths and typically affecting the superior and dorsolateral frontal cortices.

**Stage II**
Normal brain weight. Multiple epicenters at the depths of the sulci with localized spread from epicenters to the superficial layers of adjacent cortex. No neurofibrillary p-tau involvement in the medial temporal lobe.

**Stage III**
Mild reduction in brain weight. Mild cerebral atrophy with dilatation of the lateral and third ventricles. Septal abnormalities. Moderate depigmentation of the locus coeruleus and mild depigmentation of the substantia nigra. Atrophy of the mammillary bodies and thalamus. Widespread p-tau pathology in the frontal, insular, temporal and parietal cortices. Neurofibrillary pathology in the amygdala, hippocampus and entorhinal cortex.

**Stage IV**
Marked reduction in brain weight with atrophy of the cerebral cortex. Marked atrophy of the medial temporal lobe, thalamus, hypothalamus and mammillary bodies. Severe p-tau pathology affecting most regions of the cerebral cortex and the medial temporal lobe, sparing the calcarine cortex. Severe p-tau pathology in the diencephalon, basal ganglia, brainstem and spinal cord. Marked axonal loss of subcortical white matter tracts.

Abbreviations: CTE, chronic traumatic encephalopathy; p-tau, phosphorylated tau.

**Table 1** | Clinical criteria for chronic traumatic encephalopathy

| Classification | Definition | Clinical examples |
|---|---|---|
| Definite | Any neurological process consistent with the clinical presentation of CTE along with pathological confirmation (tauopathy ± diffuse amyloid deposition ± TDP-43 deposition) | Cognitive, behavioural, and/or motor dysfunction |
| Probable | Any neurological process characterized by two or more of the following conditions: cognitive and/or behavioural impairment; cerebellar dysfunction; pyramidal tract disease or extrapyramidal disease; clinically distinguishable from any known disease process and consistent with the clinical description of CTE | Cognitive impairment and extrapyramidal dysfunction suggestive of parkinsonism<br>Associated cerebellar dysfunction that is inconsistent with parkinsonism |
| Possible | Any neurological process that is consistent with the clinical description of CTE but can be potentially explained by other known neurological disorders | Alzheimer disease or other primary dementia<br>Parkinson disease<br>Primary cerebellar degeneration<br>Wernicke–Korsakoff syndrome<br>Amyotrophic lateral sclerosis |
| Improbable | Any neurological process that is inconsistent with the clinical description of CTE and can be explained by a pathophysiological process unrelated to brain trauma | Cerebrovascular disease<br>Multiple sclerosis<br>Brain neoplasm<br>Other inherited neurological disorders |

Abbreviations: CTE, chronic traumatic encephalopathy; TDP-43, TAR DNA-binding protein 43.

period of latency.[56] Four categories of clinical criteria for CTE have been defined (Table 1).

To be classified as 'definite CTE' a case must present with neurological signs that are consistent with CTE and have pathological confirmation of tau deposition with or without deposition of amyloid or TAR DNA-binding protein 43 (TDP-43). Given the lack of established consensus criteria for the neuropathological classification of CTE, the two classification schemes described above[45,51] can aid in diagnosis of definite CTE.

'Probable CTE' is defined as any neurological process involving two or more of the following clinical conditions: cognitive and/or behavioural impairment, cerebellar dysfunction, pyramidal tract disease and extrapyramidal disease. This syndrome has to be clinically distinguishable from other neurological disorders and must be consistent with the clinical description of CTE. Neuroimaging studies can provide evidence in support of probable CTE. Using $^{18}$F-FDDNP PET—a neuroimaging tool to measure tau and amyloid deposition in the brain—increased subcortical and cortical signals were detected in five retired National Football League players who exhibited cognitive and behavioural symptoms.[57] However, as $^{18}$F-FDDNP binds both fibrillary tau and amyloid, increased $^{18}$F-FDDNP signal cannot be solely attributed to tau, and additional histopathological confirmation is, therefore, needed. A negative amyloid PET scan could be useful in ruling out preclinical, prodromal or overt AD.[58] Evidence of glucose hypometabolism on PET, or hypoperfusion on single-photon emission CT (SPECT), can also support a diagnosis of CTE (discussed below). Other neuroimaging findings that are supportive of probable CTE include nonspecific evidence of CNS trauma on structural imaging and/or DTI. In one case of a 50-year-old boxer with dementia and probable CTE, CSP presented as thinning and marked loss of fibre-tract integrity in the corpus collosum (Figure 2; B. D. Jordan, unpublished work).

The category of possible CTE involves brain pathology that cannot be reliably distinguished from other primary neurodegenerative disorders such as AD, frontotemporal dementia, vascular dementia, normal pressure hydrocephalus, multiple system atrophy, and Parkinson disease-related dementia. Cases of CTE and AD co-occurrence are well-documented[45] and, therefore, despite ancillary findings such as a positive amyloid PET scan, biparietal and/or bitemporal hypometabolism on glucose PET, elevated tau and/or decreased amyloid in the cerebrospinal fluid, co-existent CTE cannot be ruled out.

Any neurological process that is inconsistent with the clinical description of CTE and exhibits a pathophysiology unrelated to TBI would be classified as improbable CTE. Examples include brain tumours, stroke and inherited neurological disorders.

As biomarkers that reflect the natural history of CTE are currently nonexistent, characterization of preclinical and prodromal CTE (which are similar to the preclinical phases that have been documented in AD)[58] is premature. However, neuroimaging biomarker abnormities, which are indicative of axonal and myelin injury, have been observed in athletes who have been exposed to repetitive brain injury. For example, in studies of professional boxers, fractional anisotropy in the corpus collosum and internal capsule was lower compared with controls,[59] and the apparent diffusion coefficient (ADC) was elevated in the cortical gray matter, and fractional

anisotropy in deep white matter was decreased compared with controls.[60] Similarly, trace radial diffusivity and axial diffusivity (purported measures of myelin and axonal pathology) increased among ice-hockey players over a season, with the damage involving regions of the corticospinal tract, the corpus collosum and the superior longitudinal fasiculus; however, no changes in fractional anisotropy were observed in this study.[61] Differences in white matter integrity have also been observed in athletes involved in soccer (a potentially high-impact sport) compared with those involved in swimming (a low-impact sport).[62]

Abnormalities on PET and SPECT have also been reported in athletes with repetitive brain injuries. A unique pattern of glucose hypometabolism was detected in the posterior cingulate cortex, parieto-occipital lobes, frontal lobes and cerebellum of boxers.[63] With the use of SPECT imaging, investigators have also observed brain hypoperfusion in the prefrontal and temporal poles, occipital lobes, anterior cingulate gyrus and cerebellum among active and retired professional American football players.[64]

### *Pathophysiology*

The pathophysiology of CTE is unknown, but is presumed to be a progressive tauopathy.[45,49] The mechanisms of phosophorylation, cell-to-cell propagation, and/or oligomerization and misfolding of tau that result in the clinical phenotype of CTE remain to be elucidated. McKee and colleagues have postulated that repetitive brain trauma and deposition of hyperphosphorylated tau protein promote accumulation of other abnormally aggregated proteins including TDP-43, amyloid-β and α-synuclein.[45] The frequency of progression from brain injury to clinical manifestation is, however, unknown, and factors that are reliably associated with progression have yet to be identified.

## Chronic postconcussion syndrome

The term CPCS is used to describe an uncommon clinical phenomenon in which the athlete experiences postconcussive symptoms that do not seem to resolve, and often results in the athlete retiring from sport. In their 2011 study, King and Kirkwilliam use the term 'permanent PCS' to characterize a condition observed in individuals from a nonathlete population who exhibited symptoms approximately 6.9 years after a concussion.[65] A substantial proportion of individuals with permanent PCS (40–59%) experienced premorbid or postmorbid conditions such as depression, anxiety, post-traumatic stress, and/or pain, which were not directly attributable to the manifestations of concussion but could exacerbate the postconcussive symptoms. In this Review, CPCS is the preferred term as the clinical labelling of symptoms as 'permanent'—which suggests that they may never resolve—could be problematic. Although no unifying definition exists with regard to the duration of symptoms that is necessary to qualify an athlete as experiencing CPCS, for the following discussion CPCS is defined as postconcussive symptoms lasting longer than 1 year.

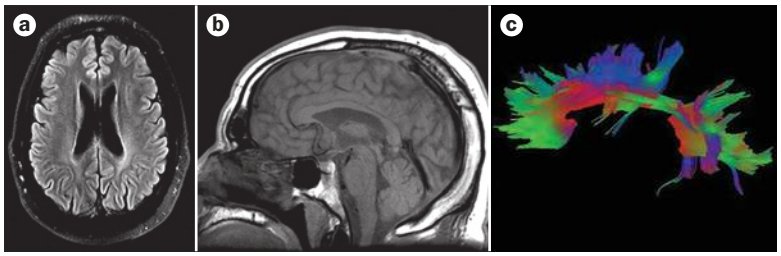


**Figure 2** | Brain imaging in a retired professional boxer with probable chronic traumatic encephalopathy. **a** | Axial T2-weighted brain MRI shows mild, diffuse volume loss, cavum septum pellucidum and cavum vergae. **b** | Saggital brain MRI demonstrates focal thinning and volume loss of the corpus collosum. **c** | Diffusion tensor imaging tractography reveals a focal defect and loss of white matter integrity in the corpus collosum.

### *Epidemiology and symptoms*

The exact frequency of CPCS among elite and nonelite athletes is unknown. In the general, nonsporting population, 10–15% of individuals are reported to remain symptomatic 1 year after concussion.[66] Common symptoms of CPCS include headache, dizziness, impaired attention, poor memory, executive dysfunction, irritability and depression. Factors associated with CPCS include older age, premorbid and postmorbid anxiety and depression, and the severity of initial postconcussive symptoms.[65]

Investigations detailing the long-term consequences of a single sport-related concussion are scarce, which may be attributable to poor detection of such injuries owing to the transient nature and rapid recovery of postconcussive symptoms.[67] The majority of CPCS cases have been reported in the lay press[68] and, as such, lack scientific scrutiny.

In 1996, Kelly and Rosenberg described a classic case of CPCS in a retired professional football player who sustained multiple concussions over a long career and exhibited persistent symptoms that were consistent with a postconcussion syndrome.[68] Persistent visuospatial attention deficits have also been reported in players of the high-impact sport Australian Rules football at least 1 year after sustaining a concussion.[69] One study reported neurocognitive and neurophysiological changes in athletes who had sustained concussions more than 30 years earlier:[67] individuals who sustained a sports concussion performed particularly poorly on tests of episodic memory and response inhibition compared with athletes who had never experienced a concussion. Evidence of motor system dysfunction among the concussed athletes included delayed and attenuated evoked potentials on an auditory oddball paradigm, a prolonged cortical silence period (an assessment of motor cortex excitability that is measured using transcranial magnetic stimulation), and bradykinesia.

### *CPCS versus CTE*

CPCS is a type of chronic TBI that is clinically distinct from CTE. Unlike CTE, CPCS has an acute onset that is temporally related to a single concussive event, and it does not present insidiously following a latent period—a defining characteristic of CTE.[45] Headache

is a prominent feature of CPCS but is not frequently encountered in CTE, with the exception of McKee stages I–II.[45] The pathological substrate of CPCS is unknown, and whether it involves the tau pathology that is classically recognized in CTE remains to be established. In addition, whether CPCS overlaps with CTE and/or represents McKee's neuropathological stages I and II[45] or Omalu's phenotype IV (incipient phenotype)[51] has yet to be explored.

## Conclusions

Acute and chronic TBI in sport represents an important public health concern in modern day society. Although brain injuries are not the most common type of sport-related injury, they can be associated with substantial morbidity and, potentially, mortality. Concussions are often unrecognized and are, therefore, underreported. Accordingly, recognition of concussion through education and proper medical surveillance is of paramount importance. Failure to adequately manage concussion could result in persistent or chronic PCS or DCS. New neuroimaging techniques may be useful in assessment of both acute and chronic brain injury. DTI, it seems, might be of greater value for evaluation of chronic ultrastructural changes following repetitive brain injury than for assessment of acute concussion or the sequelae of a single mild concussion.

CPCS is a relatively uncommon condition among athletes that needs to be further elucidated to determine whether it is causally linked to CTE or represents a distinct comorbid condition. The neuropathological substrate of CPCS in athletes is unknown and warrants further investigation.

The fact that antemortem diagnosis of CTE is difficult and that this syndrome can mimic other primary neurodegenerative disorders and has an insidious onset (typically manifesting only after an athlete has retired from sport) is of major concern. The exact frequency of CTE in athletes is unknown and, to date, the strongest putative risk factors for CTE are increased exposure to injury and older age. No reliable biomarkers currently exist to effectively diagnose CTE and monitor disease progression. At present, a definitive diagnosis of CTE can only be ascertained at autopsy, and the clinical diagnosis of CTE can only be 'probable' or 'possible'. Future advances in neuroimaging will hopefully assist in the diagnosis of this complex disorder, and *in vivo* documentation of tau deposition in the brain could potentially be used to identify athletes with a progressive tauopathy as a result of repetitive sports-related TBI.

### Review criteria

Articles were obtained through reference-list searches, cited reference searches, and regular review of sports medicine, brain injury, rehabilitation, neurotrauma, neurological and neurosurgery journals. A PubMed biomedical literature search using the key words "sports concussion", "sports-related traumatic brain injury", "chronic traumatic encephalopathy", "chronic traumatic brain injury", "second-impact syndrome", "malignant cerebral oedema", "diffuse cerebral swelling", "postconcussion syndrome", "dementia pugilistica", and "punch-drunk syndrome" was also performed. Articles included full-text papers and abstracts written in English as well as book chapters and texts. There were no restrictions on the dates of the publications.


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