What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes?

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ABSTRACT
Objective The purpose of this paper was to review the current state of evidence for chronic traumatic encephalopathy (CTE) in retired athletes and to consider the potential differential diagnoses that require consideration when retired athletes present with cognitive and psychiatric problems.

Data sources MEDLINE, CINAHL, EMBASE, Mosby’s Index, PsycEXTRA, PsycINFO and Scopus. Key words included CTE, dementia pugilistica, punch drunk syndrome, traumatic encephalopathy, CTE, repetitive head injury, sports concussion, multiple concussions, chronic concussions, subconcussive blow and sports-related traumatic brain injury.

Results At present, there are no published epidemiological, cross-sectional or prospective studies relating to modern CTE. Owing to the nature of the published studies, being case reports or pathological case series, it is not possible to determine the causality or risk factors with any certainty. As such, the speculation that repeated concussion or subconcussive impacts cause CTE remains unproven. The extent to which age-related changes, psychiatric or mental health illness, alcohol/drug use or coexisting dementing illnesses contribute to this process is largely unaccounted for in the published literature.

Conclusions At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. The causal assumptions require further prospective or longitudinal studies on the topic.

INTRODUCTION
Considerable attention surrounds the potential for long-term problems in athletes with high exposure to head impacts during a career in collision sport.1 There is evidence2–4 supporting an association between long-term cognitive, neurobehavioural, psychiatric problems and participation in sport.5 Given that sports-related concussion is a common injury and that concussive or subconcussive blows to the head or body are an inevitable consequence of sports participation, if a causal relationship between these impacts and later-life neuropsychiatric disease exists, then potentially an enormous number of retired athletes would be at risk.6 Based on the published case studies, however, one estimate is that fewer than 4% of retired US professional football players may be at risk for this condition7 rather than all exposed athletes, raising the issue that this may not be a part of impact exposure but rather due to other as yet unidentified factors.

A recent report by McKee et al8 has suggested that chronic traumatic encephalopathy (CTE) may represent a unique tauopathy with characteristic pathological stages; however, the published methodology does not allow a causal relationship to be determined between concussion or subconcussive impacts being a risk factor for CTE.

The purpose of this paper was to review the current state of evidence for CTE in retired athletes and to consider the potential differential diagnoses that require consideration when retired athletes present with cognitive and psychiatric problems.

METHODS
Articles were retrieved via online database searching, hand-searching reference lists and cited reference searches. The online databases of MEDLINE, CINAHL, EMBASE, Mosby’s Index, PsycEXTRA, PsycINFO and Scopus were searched. Key words, MeSH terms and combinations of these were used to systematically search the databases. Key words included CTE, dementia pugilistica, punch drunk syndrome, traumatic encephalopathy, CTE, repetitive head injury, sports concussion, multiple concussions, chronic concussions, subconcussive blow and sports-related traumatic brain injury (TBI).

CLINICAL SYNDROMES OF LONG-TERM PROBLEMS FOLLOWING CONCUSSION
The clinical characterisation of the presentations of athletes with chronic postconcussive symptoms is poorly defined and may reflect intrinsic differences (eg, genetic) between individuals rather than the oversimplified understanding that these syndromes are due to concussive or subconcussive trauma alone. In some cases, the persistent ‘postconcussive’ symptoms may, in large part, be due to unrecognised depression or anxiety,9 which may be labelled as ‘overtraining’ or even athlete ‘burnout’.10

If we assume concussion is the acute clinical syndrome with 90–95% of cases recovering in less than 10 days, then there is a small group where prolonged postconcussive symptoms exist, that is, where the symptoms persist more than 10 days after a single episode of acute concussion (5–10% of cases) but full recovery eventually ensues usually within a matter of weeks.11 The clinical and neuropsychological features are those of a resolving acute psychological features are those of a resolving acute
from concussive injury. These subsets are based on clinical experience and are not supported by hard scientific evidence at this time. Nevertheless, it may be useful to consider the full spectrum of presentations of athletes with persistent or permanent symptoms and the terminology of these states.

These include:

- Prolonged postconcussive symptoms as discussed above.
- Persistent postconcussive symptoms after one or more concussions where recovery is slow and may take months to years. The DSM-IV criteria for Post Concussion Syndrome is invoked only if the symptoms last beyond 3 months. Approximately 80% of such patients recover fully with time. Cognitive testing reveals mainly attentional deficits, and structural neuroimaging is normal.
- Permanent PCS—as per above, but these individuals do not recover fully, and this has been estimated at between 10% and 20% of all cases of persistent concussion symptoms. Functional MR and/or electrophysiological change may be present, but normal structural neuroimaging is typical.
- Proposed CTE where chronic cognitive and/or neurobehavioural dysfunction exists and a pathological diagnosis is subsequently confirmed. It is worth noting that there are cases where the clinical phenotype is the same as pathologically confirmed CTE cases; however, no neuropathological change is demonstrated at autopsy.

As well as these broad categories, there are other athletes who develop mental health issues (depression, anxiety, suicide) or neurobehavioural problems in the absence of persistent or prolonged concussive symptoms dating from the time of injury. Whether these represent a variant of the subsets above or prolonged concussive symptoms dating from the time of injury, and recovery following injury, and to facilitate the accurate classification of severity. For example, little is known about the anatomical localisation of common clinical features such as headache, loss of consciousness (LOC), difficulty with concentration, sleep disturbance and fatigue. Moreover, it is currently unknown whether mild TBI reflects a single clinical entity with a linear spectrum of injury or even distinct injury subtypes. It is hoped that this understanding may give some insight into whether in vivo diagnosis of CTE is possible.

In animal models following acute injury, the release of neurotransmitters and ionic fluxes occurs (known as the 'neurometabolic cascade'), which in turn leads to changes in cell membrane function. Animal studies suggest that, during the glucose metabolic depression phase (1–10 days postinjury), the brain is more vulnerable to repeat injury. Changes in the intracellular fluid status or the presence of axonal swelling may be detected using imaging techniques such as advanced diffusion-weighted imaging (DWI), which also allow mapping of white matter fibre tracts in the central nervous system. Preliminary studies have demonstrated DWI changes in the acute setting following mild TBI in a small cohort of adolescent patients with normal CT scans as well as in a cohort of asymptomatic professional boxers. Functional neuroimaging techniques, for example, functional MRI (fMRI) have demonstrated changes in brain function following sport-related TBI. The main limitation of this technique is that it only reveals regions of the brain that are active in the specific cognitive task being studied. Another imaging modality, Functional Connectivity, is able to detect real-time resting state networks and may provide an alternative to fMRI for identifying brain subregions and networks that are affected in mild TBI. Other techniques such as MR spectroscopy (MRS) allow the detection of metabolic disturbances following mild TBI through the measurement of intracellular metabolites. Preliminary studies in a small cohort of collegiate athletes suggest a role of mitochondrial dysfunction in the postinjury metabolic depression. Other studies using MRS have also demonstrated that the N-acetylaspartate/creatinine ratio (which reflects neuronal cell damage) is related to injury severity and outcome even when white matter appears normal on MRI.

DEPRESSION RATES IN THE GENERAL POPULATION

Given that cognitive impairment is one of the key features of the proposed CTE, it is important to understand the risk of this in similar age groups in the general population. The reported incidence and prevalence rates of dementia vary according to the population studied, and prevalence approximately doubles every 5 years from the age of 65 years. The incidence of dementia (all causes) in the 30-year-old to 64-year-old group is 54/100,000, and for the 45-year-old to 64-year-old group, it is 98.1:100,000. Whether mild, or repetitive mild TBI (mTBI) increases an individual’s risk for developing Alzheimer’s disease (AD) has been a long-standing topic of contention. While mixed results have been reported regarding the association between moderate and severe TBI and AD, the association between mTBI and AD appears to be less strong. For example, in a systematic review, Bazarian et al concluded that there was limited support for the notion that mTBI (with LOC) results in an increased risk for later life AD. Further, the authors also concluded that there was insufficient evidence to determine whether an association between mTBI (without LOC) and AD exists.

DEPRESSIVE, COGNITIVE IMPAIRMENT AND NEURODEGENERATIVE DISEASES IN FORMER ATHLETES

In a study of retired National Football League (NFL) players, responses to questions regarding clinical depression revealed that 269 (11.1%; 95% CI 9.9% to 12.3%) of 2434 respondents reported a previous diagnosis of clinical depression. In comparison to retired NFL players with no history of concussion, retired players with a history of one or two previous
conclusions were 1.5 times more likely to be diagnosed with depression, while those with a history of three or more previous concussions were found to be three times more likely to be diagnosed with depression.15

The results of a screening survey of 513 retired NFL players (average age=61 years) reported that 35% produced scores suggesting a possibly mild cognitive impairment.2 In another recent study of former NFL players, the death rate from neurodegenerative diseases was three times greater than that of the general population, although the number of cases in this study was small. More specifically, the rates of diagnosis of AD and amyotrophic lateral sclerosis (ALS) were found to be four times higher in former NFL players than the general population.10 Of the 334 former athletes in this cohort, seven (2.1%) had ALS listed on their death certificates. This issue of ALS is in keeping with the TDP43 tauopathy seen in CTE cases.31

**BRAIN PATHOLOGY IN NORMAL AGEING**

The Honolulu-Asia Aging Study provides a unique longitudinal model of ageing and disease and offers considerable insight into what may be considered normal ageing from a pathological standpoint.32 From 1991 to 1993, 3 yearly follow-up clinical and formal neuropsychological examinations have been conducted in 3508 men who were free of dementia and a total of 593 standardised brain autopsies have been conducted.32

Postmortem brain examination demonstrated diverse pathology, even in individuals clinically diagnosed as ‘pure AD,’ with fewer than 50% demonstrating the typical pathological features of AD. Furthermore, neuropathological abnormalities were also observed in approximately 40% of neuropathologically normal patients.32–34 Similarly, disparity between clinical presentation (ie, living diagnosis) and postmortem neuropathology has also been demonstrated in other ageing study samples.35 36 It is now clear from these ageing studies that postmortem findings may not represent pathology and may not equate to clinical symptomology or a syndrome37 and may be seen in cognitively normal older adults. Whether the ‘gold standard’ of neuropathology in neurological disease is true has been recently questioned.38

**THE ‘CLASSIC’ SYNDROME OF CTE IN PROFESSIONAL BOXERS**

In 1928, Dr Harrison Martland first described the ‘punch drunk’ or CTE state in retired boxers.39 The incidence of classic CTE has proven difficult to establish, due, in the main, to a lack of prospective studies. Roberts40 who randomly sampled 250 retired boxers from a cohort of 16 781 UK boxers registered between 1929 and 1955, reported that in 37 boxers (17%) clinically demonstrable lesions of the nervous system were present. Notably, the oldest boxers in this cohort fought in the late 1800s, in an era where bare-knuckle championships were still conducted, frequent fights occurred even when boxers were concussed and there was little medical supervision or weight matching of boxers; however, only 11 of the 37 cases were elaborated on in this study. A close analysis of the clinical details raises suspicion regarding the certainty of the diagnosis of CTE in most cases.41

In the published cases, cognitive deterioration was typically detected 10–20 years subsequent to cessation of exposure to repetitive head trauma (ie, postretirement).6 Interestingly, in all cases where details were provided, the physical signs but not the cognitive deficits progressed postretirement. There are two distinct clinical syndromes that have been demonstrated in this data set; the first (which occurs in approximately 70% of cases) includes dysarthria, pyramidal problems and cognitive deficits. As the disease manifests clinically, these cognitive abnormalities include difficulties in memory, information processing speed, insight and orientation. The second clinical syndrome (in approximately 30% of cases) includes dystarthritis and pyramidal problems, but with intact cognitive abilities.40–44 Movement disorders were reported to be present in approximately two in every five reported cases.3

One of the difficulties of ascribing the clinical syndrome solely to boxing is the presence of comorbidities plus risk factors for other conditions that may also result in cognitive deterioration. A case report of a champion boxer with cognitive decline highlights these issues of multifactorial causation of cognitive problems.45

The neuropathological features of classic CTE have been described in detail46 and typically result in a cavum septum pel- lucidum with septal fenestration; cerebellar scarring involving Purkinje cell loss and thinning of the granular layer; degeneration of the substantia nigra and locus caeruleus; and diffuse neurofibrillary tangles (NFT) involving the medial temporal region, uncus, amygdala, hippocampus, parahippocampal gyrus and fusiform gyrus along with the more lateral temporal, insular and frontal cortices. The extent of neuropathology appears to be positively correlated with the level of exposure.46 Roberts et al44 examined 14/15 brains originally described by Corsellis et al,46 as well as six additional boxers’ brains using immunocytochemistry, and 19/21 cases also demonstrated widespread diffuse amyloid deposits. Recently, a propagation model of neurodegeneration has been proposed, suggesting that tau positive NFT phosphorylation may progressively spread from one neuron to adjacent neurones in the absence of ongoing triggering factors.47–50 The implication of this finding is that the neuropathological findings may differ or progress in different stages of the condition. This finding may help resolve the differences between reports of specific sites of tau positive NFT deposition in CTE and other studies that suggest widespread changes.

**THE ‘MODERN’ SYNDROME OF CTE IN FOOTBALLERS**

Recent publications51 on CTE in retired athletes have introduced a number of conceptual changes in the clinical features52 53 and outcomes, and also the neuropathology, as compared with the classic entity described by Roberts40 and Corsellis et al46 in their boxing subjects.

**PUBLISHED MODERN CTE CASES**

A number of cases of CTE in retired athletes have been published. The index case was reported by Omalu and colleagues in 2005, with additional cases reported subsequently.4 51 54–56 Recently, the Boston University group published their experience of CTE, with 80 athlete brain donors (22 of whom were also military veterans) with a history of repetitive brain injury, and they found that 80% of these cases demonstrated the characteristic pathology for CTE.8

**Signs and symptoms**

The modern CTE description suggests that symptoms such as gait disorders, speech slowing and extrapyramidal signs may be present; however, neuropsychiatric and behavioural symptoms tend to predominate early.57 The most common symptoms reported are mood disorder (mainly depression), paranoia, agitation, social withdrawal, poor judgement and aggression. Cognitive impairment tends to emerge as the major neuropsychiatric feature in the latter stages58 59 and typically includes impairment across the domains of orientation, memory,
language, attention, information processing speed and executive functioning. These cognitive symptoms have been proposed to progress in a somewhat predictable manner, whereas the classic CTE entity reported little progression of cognitive deficits.

Neuropathology
The reported neuropathological characteristics of both entities (classic and modern CTE) appear to be more closely related and share a number of common features such as fenestrated septum pellucidum, cerebral atrophy, tau+NFT inclusion (although found in greater amounts in modern CTE), β-amyloid deposition (found in less amounts in modern CTE), reduced pigmentation of the substantia nigra and locus caeruleus, and enlarged ventricles. The qualitative description of modern CTE characterises the neuropathological change as also including fronto-temporal lobe atrophy with extensive tau pathology distributed throughout the neocortex, medial temporal lobe, diencephalon, brainstem and spinal cord. In the 51 cases reviewed by Gavett et al, diffuse amyloid plaques were found in 24 (47%), neuritic amyloid plaques in 13 (27%) and amyloid angiopathy in 3 (6%). In the Boston study, amyloid deposition was noted in 44% of the CTE cases.

Although a number of similarities in neuropathological findings have been reported across the modern CTE cases, there are also some important differences. McKee et al have reported a marked accumulation of tau-immunoreactive astrocytes, but this has not been observed in any of the cases examined by Omalu et al. Omalu et al have reported the skip-phenomenon, with a propensity to lobar cortical distribution in the absence of prominent periventricular topographic distribution, which has not been described in the McKee et al cases.

A defining neuropathological feature of the modern CTE entity is abundant filamentous tau lesions, of which the patterns of expression are considered unique, occurring in the absence (or at least relative scarcity) of β-amyloid deposits. Pronounced filamentous tau inclusions and brain degeneration in the absence of β-amyloid deposits are also considered the sine qua non of a number of neurodegenerative tauopathies. It is worth noting that a number of the degenerative tauopathies, such as behavioural variant fronto-temporal dementia, share many of the clinical and pathological features of ‘modern’ CTE.

The extent to which age-related changes, psychiatric or mental health illness, alcohol/drug use or coexisting dementing illnesses contribute to this process is largely unaccounted for in the published literature. In addition, consideration for the potential genetic risk in those athletes with a family history of neurodegenerative disease and the extent to which this contributes to the clinical and pathological profiles also require further investigation.

SUMMARY
At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. The causal assumptions require further prospective or longitudinal studies on the topic. Ultimately, scientific research might establish that participation in contact sports leads to a distinct neuropathological syndrome, and this neuropathology causes psychiatric, cognitive and physical problems, but this cause and effect relationship remains to be shown scientifically.

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