

Sports Concussion and the Risk of Chronic Neurological Impairment

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Abstract: Intense recent media focus on long-term outcomes from sports concussion has highlighted concerns on both cognitive deterioration and mental health issues, such as depression and suicide. At this time, the scientific evidence to support these views is limited, with only a handful of cases thus far reported. Based on the literature on this topic that extends back over 50 years, it is clear that only a small percentage of athletes suffer such sequelae presumably due to recurrent concussive or subconcussive head impacts. At this stage, determining which athletes are at future risk is not possible; however, following existing concussion guidelines (eg, Zurich guidelines) is likely to be the safest option based on current evidence.

Key Words: sports concussion, neurological impairment

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INTRODUCTION

Media reports have highlighted the concern that recurrent mild traumatic brain injury (TBI) or concussion in athletes may result in long-term cognitive decline or other mental health problems.¹ Although the recent interest in chronic traumatic encephalopathy (CTE) in American footballers and wrestlers has been highlighted as a novel risk, in fact, the history of scientific study into chronic brain injury in athletes extends back over a number of decades, and many historical observations are just as pertinent for the understanding of such injuries in modern athletes. What remains unclear is whether all athletes who suffer recurrent concussive or subconcussive brain impact are equally at risk of such sequelae or more likely that a subset of athletes, presumably with a genetic predisposition, are at a higher risk of CTE.

Although professional boxing in the minds of most readers represents the sine qua non of chronic brain injury, CTE has been posited in a number of other sports and activities with varying supporting clinical and pathological evidence in support of this premise.² Published reports of cases include

professional wrestling, football (soccer), rugby, skydiving, horse racing and also a professional circus clown.^{3–10}

Given the high number of sporting concussions, estimated at up to 3.8 million per annum in the United States alone,¹¹ the potential exists for significant numbers of CTE cases even if it is a relatively rare syndrome. The concept of sport-related CTE, although not new, raises fresh concern as to how such acute injuries should be safely managed to prevent the development of such uncommon sequelae.

EARLY CLUES IN PROFESSIONAL BOXERS

Although boxing as a sport dates from antiquity, it was only in 1928 that Harrison Martland first described a syndrome in prizefighters that was known in lay boxing circles as the “punch-drunk” or “slug nutty” state.¹² His article recorded 23 cases, of which he had personally examined 5, described to him by a boxing promoter. Other authors of the era further elucidated the clinical features of this condition that was successively labeled dementia pugilistica,¹³ traumatic encephalopathy, or the currently preferred term of CTE.¹⁴

The incidence of CTE in boxing is difficult to establish with any precision.¹⁵ In part, this reflects the lack of prospective studies in boxers and a change in the culture of boxing over the past century with a reduced exposure to potentially damaging head blows.¹⁶ The best estimate of the prevalence of CTE is the study of Roberts,¹⁷ who randomly sampled 250 retired boxers from a total of 16 781 UK boxers registered between 1929 and 1955. In 37 boxers (17%), clinically demonstrable lesions of the nervous system were present, and Roberts provided clinical details for 11 of the 37 cases only. It is worth noting that professional boxing as practiced in the first half of the past century, when this study was performed, is vastly different from the current day sport.¹⁵

THE CLINICAL SYNDROME OF CHRONIC TRAUMATIC ENCEPHALOPATHY IN BOXERS

The clinical syndrome of CTE is a constellation of symptoms due to lesions affecting the pyramidal, cerebellar, and extrapyramidal systems. In the mildest cases, the symptoms include a slurring dysarthria that may or may not be accompanied by subtle pyramidal disease or disequilibrium. In the latter stages, cognitive impairment becomes the major neurological feature. Throughout the course of the condition, various neuropsychiatric and behavioral symptoms may occur.^{17–23} The published clinical evidence does not support the concept that this condition goes through a predictable and

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sequential series of stages, although approximately one-third of cases are progressive in nature.^{20,23,24}

Clinically apparent cognitive deterioration in this setting tends to occur 10 to 20 years after retirement from the ring and the cessation of exposure to repetitive head trauma. Neuropsychological studies of former and active boxers suffering from CTE have found difficulties in memory, information processing and speed, finger tapping speed, attention and concentration, sequencing abilities, and frontal executive functions, such as judgment, abstraction, reasoning, planning, and organization.^{17,19,25–32} Neuropsychological abnormalities correlated significantly with the number of professional bouts, presence of abnormal computed tomographic (CT) scans, or both.^{26,27,31,33}

RISK FACTORS FOR CHRONIC TRAUMATIC ENCEPHALOPATHY IN BOXERS

The incidence and severity of CTE correlate with men who began fighting in their teens and had had several hundred professional fights.^{17,19} had a 10-year or longer boxing career,^{17,19,25,34} and were “nonscientific” boxers known for taking a punch.^{9,14,17,19} With some exceptions,^{32,35} most studies show a greater relationship of CTE to more than 20 professional bouts than to the number of knockouts.^{17,25,27,33,36}

PROPOSED ETIOLOGY OF CHRONIC TRAUMATIC ENCEPHALOPATHY IN BOXERS

It has been traditionally assumed that boxers who become punch drunk do so because of recurrent subconcussive head blows.^{8,9,12,14,23,24,37–39} It would seem, however, that this view is over simplistic in its understanding of the problem.

Other factors are likely to play a key etiological role in CTE. One published study shows that male boxers who have 12 or more professional fights and the ApoE4 allele are twice as likely to have severe deficits than similar men without the ApoE4 allele.³⁴ The assumption that boxers with CTE had neuropathological changes akin to Alzheimer disease⁹ led to research attempting to link ApoE4 to boxing injuries. In a nonboxing population, the ApoE4 polymorphism has also been shown to be significantly associated with death and adverse outcomes after all levels of acute TBI.^{40–42}

Published findings consistently suggest that head injury acts as a trigger for the deposition of amyloid- γ protein predominantly in patients with ApoE4.^{41,43} However, amyloid- γ protein deposition occurs in some patients only with head injury. There is also a possibility that head injury-related amyloid- γ protein deposition in those who survive severe head trauma may be followed by the development of the full spectrum of Alzheimer disease pathology later in life.⁴⁴ In a case study of a professional retired boxer, progressive neuropsychological cognitive decline began 37 years after his last bout.⁴³ This boxer had prominence of amyloid- γ protein-associated pathology and possessed the ApoE4 allele.

PATHOGENESIS OF CHRONIC TRAUMATIC ENCEPHALOPATHY IN BOXERS

Geddes et al⁴⁵ examined the brains of 4 young men aged 23 to 28 years, all of whom suffered mild chronic brain injury.

Pathological findings were of neocortical perivascular neurofibrillary tangles and neuropil threads. It seemed that repetitive head injury in young adults may initially be associated with neocortical neurofibrillary tangle formation in the absence of amyloid β -peptide deposition. In addition to the perivascular location, there may be diffuse neurofibrillary tangles found in the cerebral cortex and temporal horn areas that may also be associated with neuronal loss.^{46,47} Similar to the neurofibrillary tangles of Alzheimer disease, the neurofibrillary tangles of dementia pugilistica are ubiquitinated,⁴⁸ have tau immunoreactivity,⁴⁹ respond to the same antisera,⁵⁰ and have high levels of aluminum and iron.⁵¹ Unlike Alzheimer disease, the neurofibrillary tangles of CTE are located in superficial layers of the neocortex rather than in deep layers⁵² and occur without neuritic plaques; however, there are β -protein immunoreactive deposits (early plaques) throughout the neocortex.^{31,49} In addition, patients with CTE may have cerebrovascular amyloid deposits.⁴⁹

Schmidt et al⁵³ compared the molecular profile of tau pathologies in CTE with those in Alzheimer disease and showed that the same tau epitopes map to filamentous tau inclusions in Alzheimer disease and CTE brains, whereas the abnormal tau proteins isolated from CTE brains are indistinguishable from the 6 abnormally phosphorylated brain tau isoforms in Alzheimer disease brains. Thus, these data suggest that recurrent brain injury may cause CTE by activating pathological mechanisms similar to those that cause brain degeneration due to accumulations of filamentous tau lesions in Alzheimer disease, and similar, albeit attenuated, activation of these processes by a single brain injury may increase susceptibility to sporadic Alzheimer disease decades after the event. Pathologically, chronic TBI shares many characteristics with Alzheimer disease (ie, neurofibrillary triangles, diffuse amyloid plaques, acetylcholine deficiency, or abnormal tau accumulation immunoreactivity).⁵⁴

NEUROPATHOLOGICAL AND RADIOLOGICAL EVIDENCE OF CHRONIC TRAUMATIC ENCEPHALOPATHY IN BOXERS

Relatively few detailed reports of neuropathological changes in ex-boxers have been performed.^{8,9,55} There have been a number of individual case reports with varying degrees of clinical and pathological information provided.¹⁵

The largest of the studies by Corsellis et al⁹ studied 15 ex-boxers (12 professional) whose brains had been collected in a pathology department brain bank and their boxing and social history sought retrospectively. These boxers had fought in the period 1900–1940, and 8 of the boxers were national or world champions in their weight division. One of the striking features of the boxers studied by Corsellis was their extraordinarily high boxing exposure. The number of bouts fought ranged from 400 to 700+, with many boxers also being involved in fighting in fairground boxing booths up to 30 to 40 fights per day over a number of years. In this study, Corsellis detailed a number of neuropathological features that have become the sine qua non of CTE.

To date, radiological imaging has been unsuccessful in demonstrating any systematic evidence of brain injury in

boxers. Early anecdotal reports have not been validated using newer technologies.⁵⁶ The largest study of CT scans in boxers is that of Jordan et al,³⁵ who reported the findings in 388 active professional boxers. Computed tomography was normal in 93% and showed “borderline” atrophy in 6%. Only 1 study has been published reporting the findings of serial CT scanning in active boxers.⁵⁷ In this study, 45 professional boxers in New York state had serial CT scans with a mean duration between scans of 31 months. Of the 45 boxers, 6 (13%) demonstrated evidence of “progressive brain injury,” with 3 boxers displaying progressive cortical atrophy (1 with bilateral parieto-occipital encephalomalacia) and 3 boxers developing a cavum septum pellucidum (CSP). The progressive CT changes were associated with having greater than 10 losses.

One of the earliest studies using magnetic resonance (MR) in boxers was by Cabanis et al.⁵⁸ They examined 12 active and 40 retired boxers (13 amateur and 39 professional). Cerebral atrophy was noted in 8 of 52, and the mammillary bodies and optic chiasm were described as “small” in 30 of 52. Levin et al⁵⁹ and Jordan and Zimmerman⁶⁰ each studied 9 amateur boxers and found no abnormal MR findings. Jordan and Zimmerman⁶¹ subsequently examined 21 active boxers (16 professional) and 1 retired professional boxer. No clear relationship of boxing exposure and radiological findings was noted. A Swedish study comparing 22 experienced amateur boxers (mean number of bouts 54) to age-matched soccer playing and athletic controls was performed.^{62–64} No significant difference was observed between the groups. Only 2 boxers had a CSP, as did 1 footballer and 3 track athletes. Other prospective studies such as those by Holzgraefe et al⁶⁵ and Butler et al⁶⁶ did not demonstrate any MR abnormalities related to boxing.

In summary, the data from a wide variety of studies in boxers who are subject to high rates of recurrent brain impact, both concussive and subconcussive, suggest that a small percentage (<20%) of participants will develop the features of CTE, and the principal risk factors for this are (1) extremes of boxing exposure, and (2) the presence of the ApoE4 allele. The neuropathological findings of CTE in this setting share many features of Alzheimer disease. At this stage, the usefulness of MR and other sophisticated imaging techniques has been relatively limited in either detecting or predicting the development of this condition.

WHAT DOES THE RECENT LITERATURE TELL US ABOUT CHRONIC TRAUMATIC ENCEPHALOPATHY?

Neuropathological Studies

Two articles by Omalu et al^{67,68} reported 2 cases of CTE in retired professional American footballers. The first case involved a 50-year-old man who had played for 17 years in the National Football League (NFL) principally as an offensive linesman. He had a history of steroid use and a cardiac history and ultimately died of an acute myocardial infarction. No history of concussion was noted in his playing career. Clinical information from family members was suggestive of a dysthymic disorder after his retirement from football.

Neuropathological analysis demonstrated diffuse extracellular amyloid plaques, tau positive neuritic threads, and neurofibrillary tangles in the frontal, temporal, parietal, occipital, insula, and cingulate cortex but none in the hippocampus or entorhinal cortex (which would be the typical finding in Alzheimer disease). His apolipoprotein E status was E3/E3. The second case was a 45-year-old man who had played in the NFL as an offensive line tackle and right guard for 8 years after a military and collegiate football career. He reported a number of concussions in his career, although it seems that only 1 of these was medically verified. Several years after retirement, he developed a fluctuating mood and personality disorder, complicated by steroid abuse, which subsequently progressed to depression and multiple suicide attempts requiring psychiatric hospitalization. He seemed to have died of ingestion of ethylene glycol. Neuropathological examination demonstrated similar changes to the previous case with the presence of neurofibrillary tangles and neuropil threads but without significant amyloid plaques. His apolipoprotein E status was E3/E4.

A recent article by McKee et al⁶⁹ reported clinical and immunocytochemical findings in 3 retired professional athletes (1 American footballer and 2 boxers) suggestive of CTE. The footballer died of an accidental gunshot wound at 45 years and had only 1 medically verified concussion (without loss of consciousness) in his football career and was never formally diagnosed with cognitive or behavioral difficulties. Although subjective memory and executive problems developed after 40 years of age, these were not reflected in objective functional assessments. One of the boxers was 80 years old at death having fought professionally for 5 years in his late teens and suffered from relatively stable cognitive difficulties throughout his life until he developed a marked cognitive deterioration after 70 years of age. He had a history of alcohol abuse and a family history of Alzheimer disease. Computed tomographic scan revealed cerebral and cerebellar atrophy. The second boxer died at 73 years of age and had a professional ring career of 48 fights including 2 world championships following a 9-year amateur career. Approximately 20 years after retirement, he developed a progressive behavioral disorder with evidence of impairment in all cognitive domains. Neuroimaging showed cerebral atrophy, a CSP, and a lacunar infarct in the left globus pallidus. He had a strong family history of dementia.

In a further line of epidemiological research looking at neurological problems in retired athletes, data suggest that the incidence of amyotrophic lateral sclerosis (ALS) is increased in association with head injury. McKee et al⁷⁰ examined 12 cases of CTE and found 3 athletes with CTE who also developed a progressive motor neuron disease with profound weakness, atrophy, spasticity, and fasciculations several years before death. In these 3 cases, there were abundant TDP-43-positive inclusions and neurites in the spinal cord in addition to tau neurofibrillary changes, motor neuron loss, and corticospinal tract degeneration. The TDP-43 proteinopathy associated with CTE is similar to that found in frontotemporal lobar degeneration with TDP-43 inclusions, in that widespread regions of the brain are affected. Akin to frontotemporal lobar degeneration with TDP-43 inclusions, in some individuals

with CTE, the TDP-43 proteinopathy extends to involve the spinal cord and is associated with motor neuron disease. This is the first pathological evidence that repetitive head trauma experienced in collision sports might be associated with the development of a motor neuron disease.

The association of sport with motor neuron disease was initially suggested in Italian soccer players,⁷¹ but the association has been noted both in case control studies and a recent meta-analysis by Chen et al,⁷² which showed a moderately elevated risk for ALS among persons with previous head injuries (odds ratio = 1.7, 95% confidence interval, 1.3-2.2). Physical injuries to other body parts, including the trunk, arms, or legs, were not related to increased ALS risk.

Neuropsychology and Neurophysiology Studies

A questionnaire-based study of 2552 retired professional American footballers by Guskiewicz et al⁷³ identified an association between recurrent concussion and clinically diagnosed mild cognitive impairment and self-reported significant memory impairments. In this study, the players had an average age of 54 years and an average professional football-playing career of 7 years. All players completed a general health questionnaire, and then a second questionnaire focusing on memory and issues was completed by a subset of 758 retired professional football players (≥ 50 years of age). Of the former players, 61% sustained at least 1 concussion during their professional football career and 24% sustained 3 or more concussions. Retired players with 3 or more reported concussions had a 5-fold prevalence of mild cognitive impairment diagnosis and a 3-fold prevalence of reported significant memory problems compared with retirees without a history of concussion. Although there was no statistical association between recurrent concussion and Alzheimer disease, there was a trend to an earlier onset of Alzheimer disease in the retired footballers than in the general American male population.

A subsequent study by Guskiewicz et al⁷⁴ looked at the association between previous head injury and the likelihood of being diagnosed with clinical depression among retired professional football players with previous head injury exposure. Using the same general health questionnaire described above in the same cohort, the authors found that 269 of all respondents (11.1%) reported having previous or current diagnosis of clinical depression. There was an association between recurrent concussion and diagnosis of lifetime depression, suggesting that the prevalence increases with increasing concussion history. Compared with retired players with no history of concussion, retired players reporting 3 or more previous concussions (24.4%) were 3 times more likely to be diagnosed with depression; those with a history of 1 or 2 previous concussions (36.3%) were 1.5 times more likely to be diagnosed with depression. The analyses controlled for age, number of years since retirement, number of years played, physical component score on the SF-36, and medically diagnosed comorbidities such as osteoarthritis, coronary heart disease, stroke, cancer, and diabetes.

A Canadian study investigated the neuropsychological effects of having sustained a sports concussion for more than

30 years before testing on cognitive and motor functions.⁷⁵ In this study, 19 healthy former athletes (mean age = 61 years), who sustained their last sport-related concussion in early adulthood (mean age = 26 years), were compared with 21 healthy former athletes with no history of concussion (mean age = 59 years). Neuropsychological tests sensitive to age-related changes in cognition were administered. In addition, P300a and P300b brain responses and motor cortex excitability were assessed. Relative to controls, former athletes with a history of concussion had (1) lower performance on neuropsychological tests of episodic memory and response inhibition, (2) significantly delayed and attenuated P3a/P3b components, (3) significantly prolonged cortical silent periods, and (4) significantly reduced movement velocity (bradykinesia). The finding that the P3, cavum septum pellucidum and neuropsychological and motor indices were altered more than 3 decades after concussion provides a suggestion for the long-term effects of cognitive and motor system changes subsequent to sports concussion. There were a number of limitations, including the self-reported injury data.

Neuroradiology Studies

Given the lack of sensitivity of conventional structural MR imaging in detecting changes of CTE in athletes with clinical symptoms, various groups have recently explored alternative neuroimaging techniques.

Kraus et al⁷⁶ used diffusion tensor imaging (DTI) to assess in vivo axonal integrity in the setting of chronic TBI. In this study, 20 mild TBI, 17 moderate to severe TBI, and 18 controls underwent DTI and neuropsychological testing. Fractional anisotropy was the primary measure of white matter integrity and was calculated from the DTI data. Cognitive domain scores were calculated from executive, attention, and memory testing. Decreased fractional anisotropy was found in all 13 regions of interest for the moderate to severe TBI group but only in the corticospinal tract, sagittal stratum, and superior longitudinal fasciculus for the mild TBI group. White matter load (a measure of the total number of regions with reduced fractional anisotropy) was negatively correlated with all cognitive domains. Analysis of radial and axial diffusivity values suggested that all severities of TBI can result in a degree of axonal impairment, whereas irreversible myelin damage was only apparent for moderate to severe TBI. The present data emphasize that white matter changes exist on a spectrum, including mild TBI. An index of global white matter neuropathology (white matter load) was related to cognitive function, such that greater white matter pathology predicted greater cognitive deficits. Mechanistically, mild TBI white matter changes may be primarily due to axonal damage as opposed to myelin damage. The more severe injuries impact both. Diffusion tensor imaging provides an objective means for determining the relationship of cognitive deficits to TBI, even in cases where the injury was sustained years before the evaluation.

In a series of articles by Chen et al, fMRI has been used to explore the neuroradiological manifestations of the post-concussive symptomatic state. Abnormal brain activation patterns in the dorsolateral prefrontal cortex were noted in symptomatic patients after concussion and the observed changes paralleled the temporal course of the clinical recovery.^{77,78} In

addition, post-concussive subjects with depressive symptoms (using the Beck Depression Inventory) showed reduced activation in the dorsolateral prefrontal cortex and striatum and attenuated deactivation in medial frontal and temporal regions. The severity of symptoms of depression correlated with neural responses in brain areas that are implicated in major depression.⁷⁹ These latter results suggest that depressed mood after a concussion may reflect an underlying pathophysiology consistent with a limbic-frontal model of depression.

WHAT DO THE STUDIES TELL US?

What is becoming increasingly clear from a number of diverse lines of research is that a small percentage of athletes seem to disproportionately suffer chronic or long-term sequelae from sports-related head injury. Interestingly, this does not seem to be confined to the brain but affects the spinal cord and other parts of the nervous system.

The central neuropathological process concerned in this deterioration involves the role of tau protein in the brain and its abnormal hyperphosphorylation in the setting of head trauma, and this process remains to be fully clarified. The role of tau gene mutations, such as those found in frontotemporal dementia with parkinsonism, may promote its abnormal hyperphosphorylation and also be a cause of neuronal loss.⁸⁰ Whether the affected athletes suffer similar genetic variations has not been established.⁸¹ This overall view conforms to an emerging picture of a shared mechanism that underlies the fundamental process(es) leading to neuronal death. Increased availability of the fibrillogenic protein substrates of the pathological aggregates that define several neurodegenerative proteinopathies (eg, α -synuclein in Parkinson disease, β -amyloid in Alzheimer disease, and tau protein in the tauopathies) contributes to causation and risk in both the familial and sporadic forms of these disorders.⁸²

Radiological, neuropsychological, and neurophysiological studies show that focal abnormalities in the brain (such as the dorsolateral prefrontal cortex) reflect post-concussive symptoms and their persistence as well as post-concussive depression. It remains to be seen whether such focal lesions correlate with the anatomical sites of neurofibrillary tangles and other pathology. Such studies will only be evident with increasing numbers of pathologically verified cases.

Although the evidence suggests that central nervous system trauma is a risk factor for CTE, as well as for other neurological diseases such as Alzheimer disease, Parkinson disease, and motor neuron disease, very little is known about what type, frequency, or amount of trauma is necessary to induce the accumulation of these pathological proteins and more importantly why only a small number of athletes are at risk for CTE.⁸³

CAN WE PREVENT CHRONIC TRAUMATIC ENCEPHALOPATHY IN ATHLETES?

The published case studies with pathologically verified CTE show that athletes do not consistently self-report or have medically verified episodes of concussion during their sporting careers. This would argue against the concept that concussion per se is the basis for this condition. This, however, may raise the possibility that unrecognized subconcussive blows have

a role to play in this injury, although this premise remains unproven at the present time.

One theme raised in the media is that return to play on the day of injury or premature return to play before full recovery may result in the development of CTE or other sequelae. The present concussion management paradigm, if correctly followed, suggests no playing or training until full clinical and cognitive recovery has occurred.⁸⁴ This management approach, coupled with annual neuropsychological assessments, would seem to be a safe and appropriate strategy, at least in the short term.⁸⁵

Although only a handful of nonboxing athletes have been reported with CTE, some of the striking associations are a positive family history of dementia, prominent neuropsychiatric symptoms, and the use of steroids/other pharmacological agents. Although the first of these tantalizingly points to a genetic association, their presence may be more important in screening athletes before participation in sport and considering counseling. If clear-cut risk factors can be recognized in an individual, then limiting the exposure of high-risk athletes to brain impact, in addition to enhanced medical surveillance, will be a key part of a comprehensive management approach.

Future prospective studies will be necessary to answer these questions and to determine at what age the nervous system is most susceptible to the deleterious effects of trauma and whether proper management of acute head injuries is effective in reducing the incidence of late-life neurodegenerative dementias. At this stage, the available evidence suggests that our management guidelines for acute concussion, if followed, are appropriate.

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