Chronic traumatic encephalopathy: a potential late and under recognized consequence of rugby union?

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Summary

The association between exposure to head injury and increased risk of neurodegenerative disease, specifically chronic traumatic encephalopathy (CTE), is widely recognized. Historically, this was largely considered a phenomenon restricted to boxers, with more recent case series identifying further ‘high risk’ individuals, such as former American footballers, or military personnel. However, in all cases thus far reported, it is clear that it is the exposure to head injury which is associated with increased dementia risk, and not the circumstances or environment of exposure. As such, there is considerable potential for under-recognition of CTE in patients presenting with neurodegenerative disease, particularly where head injury exposure might have been historical and through sport. This article reviews current understanding of CTE and, via an illustrative case in rugby union, highlights the value of a detailed history on head injury and also draws attention to imaging studies in assessing patients with neurodegenerative disease.

Introduction

Concussions are a frequent occurrence in contact sports, with an estimated 1.6–3.8 million sports-related mild traumatic brain injury (mTBI)/concussions annually in USA.¹ In recent years, there has been an explosion in interest in the long-term outcomes of sports-associated brain injury. Specifically, there is growing awareness of the association between exposure to repetitive mTBI and increased risk of neurodegenerative disease, in particular chronic traumatic encephalopathy (CTE), through reports of CTE in former athletes from a range of contact sports and in exmilitary personnel (for review).²

In current understanding, CTE is associated with gradual onset of neuropsychological, psychiatric and behavioural disturbance followed by progressive cognitive decline.³,⁴ To date, no clinical diagnostic criteria have been established and, as such, autopsy examination with detailed neuropathological review remains the only means to establish the diagnosis. At autopsy, a degree of cortical atrophy may be present, with abnormalities of the septum pellucidum also described, specifically cavum septum pellucidum (CSP) or septal fenestration.²,⁴ Microscopy reveals a mixed pathology, typically featuring deposition of abnormal, hyperphosphorylated forms of the microtubule associated protein tau in a distinctive pattern and distribution which assists differentiation of CTE from other tau-associated pathologies.²,⁵,⁶,⁷ Nevertheless, despite increasing recognition of the association between mTBI/concussion and CTE, confirmed cases remain few, perhaps as confirmation still rests with autopsy examination and there remains limited awareness in clinics that the condition occurs in sports outside of boxing. However, common to all cases described, thus far, is a history of exposure to repetitive head impacts with mTBI / concussion.
Herein, by way of illustration, we present the first comprehensive case report of CTE in a former amateur rugby union player in whom the diagnosis in life was unclear, but confirmed as CTE at autopsy. The implications of this case and our current understanding of CTE are then reviewed.

Case report
Ethical approval
The Dublin Brain Bank programme is approved by the Ethics Committee of The Royal College of Surgeons in Ireland, with specific consent for research tissue usage and for publication obtained from the patient’s next of kin.

Clinical history
A 56-year-old businessman first presented in 2011 following an apparent acute confusion episode where he was unable to find his way home. On closer enquiry, a 5-year history of gradually progressive attention, memory and organizational difficulties was elicited, leading to difficulty managing his previously successful business which, as a consequence, had run into financial difficulties.

His mother had developed a psychotic depressive disorder in her 70s and died 10 years later with mild cognitive difficulties. A maternal uncle had late onset Alzheimer disease. The patient was a non-smoker, had consumed 20–30 units of alcohol weekly. Past medical history was notable for asthma, hypertension, hypertrophic cardiomyopathy, gout and left myringotomy. Medications were ramipril, aspirin and atorvastatin.

Of note, the patient was a former rugby union prop forward, with a notably long playing career which extended from early teens to his last game at age 50; participating prior to professionalization to senior provincial level, and just below international standard. On retrospective enquiry from first-degree relatives, it was reported that, throughout his rugby career, he experienced countless head injuries with features in keeping with mild TBI/concussion, though none required hospitalization. In addition to this sports-associated exposure to TBI, there was a single work-related head injury, without loss of consciousness, as a consequence of being struck by falling scaffolding; again formal medical attention was not required. There was no history of boxing, martial arts or other notable contact sports participation.

Neurologic examination
Positive examination findings at presentation included axial rigidity, hypomimia, positive glabellar tap and the ‘around the houses’ sign of hypometric vertical saccades, asymmetrical upper limb rigidity, bradykinesia and ideomotor apraxia. Cognitive examination performed using the Montreal Cognitive Assessment (MoCA) yielded a score of 17/30. There was a dysexecutive–amnestic pattern with sparing of the orientation, naming, repetition and digit-span components of the MoCA but marked difficulty with the trail-making, cube copy, serial 7s, verbal fluency and recall components.

Imaging studies
Initial reports of magnetic resonance imaging at presentation described age-related white matter changes, with no other significant observations. However, retrospective review of imaging prior to autopsy identified anteriorly cavum, posteriorly fenestrated septum pellucidum, together with bilateral increased signal intensity in the hippocampi in keeping with gliosis (Figure 1a, b). A dopamine transporter scan at diagnosis revealed reduced accumulation of isotope in the caudate and putamen nuclei bilaterally, with 18F-FDG-PET demonstrating evidence of frontal and posterior cingulate hypometabolism.

Initial diagnosis and clinical course
He was initially diagnosed as dysexecutive mild cognitive impairment. However, over the subsequent year, there was progression of cognitive symptoms and the emergence of Parkinsonism, with axial rigidity and abnormal vertical saccades. Because a clinical diagnosis of progressive supranuclear palsy (PSP) was made. A trial of levodopa and carbidopa was unsuccessful.

Over the following months, he experienced continued symptom progression, requiring admission to hospital because of further acute confusion episodes and increasing falls. He continued to deteriorate to his death from respiratory failure secondary to aspiration pneumonia at age 57, a year after first neurologic presentation and an estimated 6 years after first symptoms.

Neuropathological findings
Gross neuropathology
External examination of the brain was unremarkable, with the weight of the intact, whole brain 1350 g. There was no evidence of focal pathology related to previous TBI, the meninges were thin and transparent and there was no evidence of sulcal widening, gyral abnormalities or external abnormalities of the cerebellum or brainstem. The vessels comprising the Circle of Willis were in the normal anatomic position and unremarkable.

Dividing the cerebral hemispheres in the midline sagittal plane confirmed a fenestrated septum pellucidum. Coronal sections of the cerebral hemispheres revealed an apparently unremarkable cortical mantle, centrum semiovale and corpus callosum. The hippocampi appeared somewhat atrophic. In the basal ganglia, there was pallor of the substantia nigra. Otherwise the caudate nuclei, putamen and globus pallidus were unremarkable. The cerebellum appeared unremarkable. Again, there was no evidence of TBI-related focal pathology.

Microscopic neuropathology
Tissue blocks were sampled using standard protocols for the assessment of neurodegenerative disease and assessed independently by two experienced neuropathologists (MF, WS) using established diagnostic criteria for neurodegenerative disorders.

The most striking observation was the presence of widespread p-tau pathologies throughout the neocortex, hippocampus and striatum in the form of p-tau-immunoreactive neurofibrillary tangles (NFT) and dystrophic neurites, with notable perivascular, subpial and sulcal depth accentuation (Figure 2a–c), and p-tau-immunoreactive neurites dispersed throughout white matter. Further, p-tau-immunoreactive profiles in keeping with immunopositive astroglia (Figure 2d) were noted, largely in perivascular and subpial locations. Coinciding with this, pathology was extensive cortical superficial linear spongiosis and profoundly atrophic hippocampi, with near total loss of neurons from the CA4, CA3 and CA2 regions, with relative sparing of CA1.
Widespread p-tau pathologies were also present in sections from the hindbrain as immunopositive NFTs in residual neurons of the substantia nigra, which otherwise showed profound depletion of pigmented neurons, together with astrocytic gliosis and pigmentary incontinence. Further p-tau positive neurites were noted throughout the white matter, in particular of the cerebral peduncles and in the cerebellar subcortical white matter, and showing periaqueductal accentuation. No PSP-like globose tangles were identified. Very rare tufted astrocytes (Figure 2e) were noted in superficial subpial cortex of the sulcal depths but not elsewhere.

In sections stained for abnormally phosphorylated-TDP (p-TDP), cytoplasmic inclusions were present in neurons of the dentate fascia, hippocampus and entorhinal cortex (Figure 3). However, no classical or cortical Lewy bodies were present in sections stained for α-synuclein and no amyloid-associated pathologies were observed in sections stained for amyloid-β.

Clinicopathological diagnosis
Chronic traumatic encephalopathy.

Discussion
This case illustrates CTE arising in a patient whose exposure to repetitive mTBI/concussion was through participation in amateur rugby union. In life, the clinical impression was of a PSP-like syndrome; the diagnosis of CTE not considered prior to death. However, after death the history of rugby participation, together with imaging review identifying CSP raised the possibility of CTE, which was subsequently confirmed on detailed neuropathology examination.

The association between exposure to TBI in sport and long-term neurological sequelae first came to note in 1928 thorough observations on the ‘Punch Drunk Syndrome’ by the New York City Medical Examiner, Harrison S Martland, in which he described a constellation of stereotypical neuropsychiatric and motor symptoms in former boxers.8 In the decades that followed, further cases were reported9-10 and detailed examinations of former boxers’ brains described a distinctive neurodegenerative pathology termed ‘dementia pugilistica’ (DP), reflecting its almost exclusivity to boxers in these early case descriptions.11,12 However, not until the recognition of this same pathology in non-boxer and military personnel did the association between exposure to repetitive mTBI and increased risk of this form of neurodegenerative disease, now more inclusively termed CTE, gain attention.

In 2005 Omalu described the first case of CTE in a former National Football League player.13 Subsequently, CTE has been described in several selected postmortem cohorts of professional and non-professional athletes including examples from American football, ice hockey and wrestling,14-17 in addition to military veterans.18,19 Despite increasing descriptions of CTE in former athletes, understanding of the incidence of this condition remains remarkably limited, with the only insight coming from studies estimating up to 17% of former boxers at risk in some series. Prior to this report, to the best of our knowledge, just a single confirmed case of CTE in rugby union has been described in a patient dying at age 71 years,20 although in that report very little information on the patient’s history, participation in rugby or investigations is provided. The current low CTE case ascertainment in rugby union may well be due to a lower frequency of CTE in rugby union. Additionally, as demonstrated in this patient, low clinical recognition of CTE might be contributing to under-reporting, with cases perhaps given alternate neurodegenerative diagnoses, including PSP.

Notably, in all cases thus far described, the only common identified risk factor is exposure to repetitive mTBI. In this regard, the incidence of concussion in elite level rugby union is reported as among the highest in contact sport,20 with so called ‘sub-concussive’ head impacts occurring as frequently in rugby union as in American Football.21 As a consequence of this perceived risk, World Rugby (formerly International Rugby Board) has introduced programmes to better manage concussion injuries and to consider introduction of measures to reduce incidence.22

The clinical features of CTE typically presents years to decades after injury exposure and span neuropsychiatric, behavioural, cognitive and motor symptoms.23 In particular, emotional lability, aggression, poor judgement and depression are described as perhaps distinctive and early clinical features of CTE. In this regard, it is notable that, although our case
presented with cognitive impairment, prior to admission he displayed symptoms of mood and behavioural disturbance, including impaired judgment, precipitating difficulties in his normally successful business affairs.

A particular feature in this case was the presence of Parkinsonian symptoms, with gaze palsy, falls and axial rigidity; hence the clinical impression of PSP was raised. However, at autopsy, PSP pathologies were not confirmed, and there was widespread neuronal loss, gliosis and p-tau pathology in the striatum and midbrain typical of CTE. Though less commonly reported in current case series of non-boxer athletes with CTE, a variety of motor symptoms, in particular Parkinsonian symptoms, are commonly described in case series of CTE in former boxers.4,8–10

Notably, on retrospective review of imaging studies after death, CSP and septal fenestration were identified, together with imaging evidence in keeping with gliosis in the medial temporal lobe. CSP represents one of the most frequent macroscopic findings in CTE, particularly in boxing-associated cases.2 However, given its presence as an incidental observation in imaging studies in ‘normal’, non-head injured populations23,24 its significance in assessing CTE is often questioned. However,

Figure 2. Representative immunohistochemical sections of the brain illustrating the pathology of CTE. In sections stained for hyperphosphorylated tau (monoclonal antibody to PHF-1; courtesy Dr P Davies), immunopositive glial and neuronal profiles were identified in a typical pattern and distribution showing (a) perivascular concentration (b) subpial accumulation with abundant NFTs and (c) at the depths of sulci, (d) Rare phospho-tau positive astrocytic plaques, (e) infrequent tufted subpial astrocytes.
from both historical accounts and more recent literature, there is evidence to support increased incidence and severity of CSP and associated septal abnormalities in patients with CTE and, whilst CSP may simply represent exposure to repetitive TBI, rather than being directly consistent with CTE, in the context of a supportive clinical history, its presence might warrant consideration of a diagnosis of CTE in a patient under investigation for a neurodegenerative disorder.

We believe this is the first comprehensive report of pathologically confirmed CTE in a former rugby union player which adds to current understanding of CTE in contact sports. In particular, the possibility of under-recognition and, with that, under-diagnosis is raised. With increased awareness of CTE, we would suggest the diagnosis might be considered in any patient presenting to dementia services with a prior history of exposure to TBI, in particular where structural imaging studies demonstrate abnormalities in the septum pellucidum.

Conflict of interest: None declared.

References