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Chronic traumatic encephalopathy — confusion and controversies

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Abstract

The term chronic traumatic encephalopathy (CTE) has recently entered public consciousness via media reports and even a Hollywood movie. However, in contrast to general impressions, the incidence of CTE is unknown, the clinical diagnostic criteria have not been agreed upon and the current neuropathological characterization of CTE is acknowledged as preliminary. Additionally, few studies have compared the pathologies of CTE with those of other neurodegenerative disorders or of age-matched controls. Consequently, disagreement continues about the neuropathological aspects that make CTE unique. Furthermore, CTE is widely considered to be a consequence of exposure to repeated head blows, but evidence suggests that a single moderate or severe traumatic brain injury can also induce progressive neuropathological changes. These unresolved aspects of CTE underlie disparate claims about its clinical and pathological features, leading to confusion among the public and health-care professionals alike.

In little more than a decade, the term chronic traumatic encephalopathy (CTE) has emerged into public consciousness via intense media coverage. The issue has even spawned numerous documentaries and is the subject of a Hollywood movie in which a neuropathologist is the protagonist[1]. This media attention has helped to increase awareness of an important public health concern but has often included inaccurate or confusing

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Author contributions

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descriptions of the fundamental aspects of CTE, thereby causing undue alarm. For example, news stories have implied a link between suicide and brain pathologies in former athletes, but no evidence supports this association. Other reports suggest that degenerative brain disease is almost inevitable for participants in some sports[2,3], but the actual incidence of CTE remains unknown[4]. Furthermore, despite the widely held impression that the neuropathology of CTE has been fully characterized, current consensus neuropathological criteria are acknowledged as only preliminary, in part because these criteria are based on a limited number of selected cases[5]. As a consequence, many disparate claims about the clinical and pathological features of CTE continue to confuse not only the general public, but also health-care professionals. Nonetheless, behind the hyperbole, a long history of CTE (FIG. 1) points the way forward to a better understanding of the association between traumatic brain injury (TBI) and late neurodegeneration.

In this Perspectives article, we examine the history of CTE from its first description as a neuropsychiatric entity in boxers through to current understanding of its neuropathological characteristics from a wide range of TBI exposures. We also address areas where the public perception of CTE and the scientific literature do not align, and the associated controversies.

History versus headlines

Although the term CTE has only recently entered the public vocabulary, an association between repeated head blows and early dementia has been recognized for over 90 years. In 1928, Martland first described the chronic neuropsychiatric sequelae of boxing as the ‘punch drunk’ syndrome[6], which was later referred to as dementia pugilistica. Multiple subsequent reports elaborated on these early observations and generated a somewhat consistent and characteristic clinical picture[7–10], which included psychiatric symptoms, emotional lability, personality changes, memory impairment and dementia, pyramidal and extrapyramidal dysfunction, and cerebellar impairment. In 1969, a comprehensive study of 224 randomly selected, living professional boxers demonstrated that 17% exhibited a “relatively stereotyped clinical pattern” consistent with a degree of neurological impairment[11].

Despite this long experience with dementia pugilistica, it has now been subsumed into CTE, a clinical entity that is more encompassing but is also more vague, a problem that has resulted in misunderstanding and controversy. Particular confusion has arisen around symptoms such as suicidality, aggression and disinhibition, which were not characterized in dementia pugilistica but have been described in contemporary series of non-boxer athletes for whom a diagnosis of CTE was made at autopsy[3,12]. This issue could be exacerbated by the fact that, at present, CTE is defined by neuropathology rather than formal clinicopathological correlation. In addition, the general perception that athletes are at increased risk of suicide and dementia associated with repetitive mild TBI-induced neuropathology seems to be based on multiple high-profile media reports rather than on evidence from adequately powered and unbiased scientific studies. Indeed, in a study of retired American National Football League (NFL) players who were followed up until 2013, the suicide rate was actually lower among this population than would have been expected among a comparable US population[13]. However, in more recent studies the reported suicide rate among individuals with autopsy-diagnosed CTE has been higher than anticipated[3]. If

confirmed, this observation could indicate a recent change in suicidality among former NFL athletes, an area that will require careful exploration. Prospective studies of athletes involved in contact sports other than boxing are currently underway, which might help to resolve the incidence of CTE and its neuropsychiatric profile, including suicidality, and determine whether these characteristics differ from those observed long ago in boxers.

Not new, just newly publicized

Despite several decades of suspicion that boxing could lead to progressive neurodegeneration, the neuropathology of a boxer with dementia was not described until the report of Brandenburg and Hallervorden in 1954 (REF.[14]). Two decades later, in a landmark autopsy study of former professional and amateur boxers, Corsellis and colleagues detailed stereotypical neuropathological findings associated with dementia pugilistica[15] that continue to be elaborated today. However, these observations raised little interest from the public or the research community, perhaps owing to the misperception that boxing is unique with regards to head impacts and repetitive mild TBI.

Despite media claims and the narrative of the movie *Concussion*[1] CTE is not a new disease entity; recognition that the condition can occur in contact sports and contexts other than boxing is what is new. In particular, neuropathological findings similar to those previously described in boxers have been reported in players of American football, ice hockey, soccer and rugby[12,16–21], and in military personnel[22,23]. In addition, identification of similar pathology in individuals who have experienced a single moderate or severe TBi[24,25] (see Neurodegeneration after a single TBI below) has drawn attention to the possibility that CTE-like pathology can be associated with the full spectrum of TBI severities.

Tangled impressions about tau

Features of tau pathology that might characterize CTE have been identified, but disagreement exists about the validity of this histopathological characterization. Current evidence suggests that the distribution of neurofibrillary tangles in TBI-associated neuro degeneration is distinct from that in other neurodegenerative diseases. In multiple accounts of CTE in the past three decades[12,16–23,26], cortical pathology has been described as a patchy distribution of hyperphosphorylated tau deposits in neurons and glia, typically in perivascular locations and with a preferential distributior towards the depths of cortical sulci. These observations form the core of the current consensus criteria for the neuropathological diagnosis of CTE[5]. However, remarkably few cases have been described in the literature, and these consensus criteria are acknowledged as being preliminary, in part because they are based on the review of autopsy samples from just ten selected individuals.

Whether the distribution of neurofibrillary tangles is sufficient to diagnose a neuropathologically distinct neurodegenerative disorder, regardless of the clinical syndrome or previous exposure to TBI, remains unclear. Notably, a review of tissue samples from the Queen Square Brain Bank (London, United Kingdom) identified the so-called pathognomonic tau pathology of CTE in 12% of individuals from whom tissue was examined, regardless of whether the individual had a history of neurodegenerative disease[27].

However, all individuals in whom CTE pathology was present in this study had previously been exposed to TBI. On this basis, the tau pathology that is currently considered as being characteristic of CTE might indicate exposure to TBI but not necessarily neurodegenerative disease per se. Furthermore, the fact that the number of cases evaluated to date is limited means that attempts to stage neurodegenerative disease on the basis of neurofibrillary tangle distribution must remain speculative[12,28]. These uncertainties are reinforced by disparities between pathological descriptions. For example, early studies of pathology in boxers identified that tau pathology was most abundant in the medial temporal lobe[15], whereas subsequent studies suggest relative sparing of the medial temporal lobe[5,12,18,19].

Tau is not alone

In contemporary reports, the designation of CTE has often been based on the presence of tau pathology alone[5]. Neurofibrillary tangles are undoubtedly one of the most consistently described pathologies in patients with CTE[12,25], but historic accounts and other contemporary case series make clear that post-TBI neurodegeneration is a multifaceted pathology (FIG. 2); the additional pathologies that have been described are discussed below. In the future, the constellation of neuropathological changes that are linked with a history of exposure to TBI will continue to expand, as has been the case for many other neurodegenerative diseases. Nonetheless, on the basis of current evidence, we might already embrace the concept that CTE is not associated with a singular neuropathology.

Amyloid-β.

Amyloid-β (Aβ) pathology has frequently been identified alongside tau pathologies in post-TBI neurodegeneration[29]. In a re-examination of Corsellis' original series with further cases added, 19 of 20 former boxers were found to have diffuse Aβ plaques[30]. Case series of non-boxer athletes have also demonstrated a high prevalence of Aβ pathology, which increases with higher age at death[3,25,31]. As such, whether Aβ pathology in CTE is directly linked to a history of exposure to TBI or is simply related to age remains to be elucidated. Notably, individuals with Aβ pathology also had clinical symptoms of cognitive impairment. Given that a limited number of cases have been examined and age-matched controls have not been used, further studies are undoubtedly required to determine the role of Aβ pathology in CTE before concluding that this pathology is incidental.

TDP43.

Evidence suggests that the 43 kDa transactive response (TAR) DNA-binding protein (TDP43) is involved in post-TBI neurodegeneration. In some conditions, TDP43 translocates from the nucleus to the cytoplasm, where it can become polyubiquitinated and hyperphosphorylated to form pathological inclusion bodies[32]. TDP43 is increasingly recognized as a major disease-associated protein in several neurodegenerative conditions, including frontotemporal lobar dementia and amyotrophic lateral sclerosis (ALS)[32,33], and as a minor component in various other conditions, such as Alzheimer disease (AD) and Parkinson disease[34–36]. Autopsy studies of former boxers, American football players and hockey players have identified neuronal cytoplasmic TDP43 inclusions and distinctive 'grain-like' profiles in the surrounding neuropil in multiple regions[5,37,38]. In a small number

of patients with ALS, autopsy studies have identified the tau pathology of CTE alongside TDP43 pathology[12,38]. However, these few observations are not enough to conclude that the observed pathology represents an ALS-like variant of CTE (a condition that has been referred to as CTE plus motor neuron disease) or simply ALS with coincident CTE-like tau pathology.

Atrophy.

Acute and chronic axon degeneration after a single, severe TBI have been extensively documented, but white matter changes after repetitive mild TBI have also been observed in association with evidence of gliosis, foci of white matter degeneration or rarefaction[15,39,40], and patchy loss of myelin staining[15,28,39,41]. Similarly, evidence of neuroinflammation has been observed, albeit in few case ser ies[15,28,40,42,43]. In addition, brain atrophy is frequently reported in boxers, often in the frontal and temporal lobes and the cerebellum[8,15,41,44,45]. In most descriptions of CTE in boxers[8,15,25,39,40,42] and in many non-boxer athletes[12,21,25], the pathologies observed include abnormalities of the septum pellucidum, including cavum septum pellucidum, which are often associated with ventricular dilatation.

Neurodegeneration after a single TBI

Substantial epidemiological evidence demonstrates that exposure to just a single moderate to severe TBI is associated with an increased risk of late neurodegeneration[4,25,46–51]. In the reports to date, which have typically been based on retrospective studies, the dementia that follows a single TBI is often classified as AD-like, although none of these studies have included confirmation of the neuropathology at autopsy. Consequently, the presumption that AD follows a single moderate to severe TBI is, at best, speculative. Nonetheless, the idea that repetitive mild TBI leads to CTE but that a single moderate to severe TBI leads to AD is often put forward[52]. However, a series of studies show that almost all of the neuropathological changes described in boxers and non-boxer athletes as a result of repetitive mild TBI can also be observed in some individuals years after surviving a single moderate or severe TBI[24,25,53,54].

Can CTE follow a single TBI?

Analysis of non-selected brain tissue samples from individuals in the Glasgow Traumatic Brain Injury Archive (United Kingdom) who survived for ≥1 year after a single moderate or severe TBI revealed a greater density and wider distribution of both neurofibrillary tangles and Aβ plaques in ~30% of patients with TBI than in age-matched controls who had not experienced a TBI[24]. However, these proteinopathies followed different temporal courses.

Pathological examination within months of a single moderate or severe TBI did not reveal the presence of any neurofibrillary tangles[55], yet abundant neurofibrillary tangles were observed beyond 1 year[24], suggesting that the processes that drive the formation of neurofibrillary tangles after TBI might progress over months to years. By contrast, Aβ pathology after a single moderate or severe TBI seems to develop much faster. Notably, in a large animal model of TBI[56] and in a study of human brain tissue[57], a unique mechanism of Aβ production after TBI has been linked to progressive axonal pathology. Specifically,

massive accumulation of amyloid precursor protein, presenilin 1 and β-secretase in damaged axons shortly after injury triggers formation of Aβ within the axon membrane compartment[58].

This extensive genesis and release of Aβ from lysing axons might account for the Aβ plaques that are seen in autopsy samples[59,60] and in surgically excised brain tissue from patients in the acute phase following a moderate or severe TBI[61]. These Aβ plaques can be observed within hours of injury and are associated with polymorphisms in the genes that encode apolipoprotein E[62] and neprilysin[63]. By contrast, few Aβ plaques are found in the brains of individuals who survive a single moderate or severe TBI several months after the injury, but beyond 1 year, plaques reappear at a higher density than in age-matched controls[24]. In these individuals, fibrillar Aβ plaques were observed in addition to diffuse plaques. Notably, chronic neuroinflammation has been observed to last for decades after a single moderate or severe TBI, in association with ongoing white matter loss and axonal degeneration[53], which might have a role in the formation of late Aβ plaques.

The TDP43 proteinopathy observed in some people who have experienced repetitive mild TBI does not seem to develop in patients who survive a single moderate or severe TBI[64] (FIG. 2). This observation raises the intriguing possibility that some pathological processes are shared across the spectrum of TBI severity whereas others differ.

Conclusions and the evolution of CTE

Ninety years since Martland's original description of the 'punch drunk' syndrome[6], numerous key questions about CTE remain unanswered. By all accounts to date, the clinicopathological heterogeneity of CTE rivals that of AD and other neurodegenerative disorders. To allow meaningful clinical research to progress, there is a pressing need to achieve consensus about the clinical and neuropathological operational diagnostic criteria for CTE. In parallel, the question of whether the pathologies that have been described after a single moderate or severe TBI are the same as the pathologies that develop after repetitive mild TBI needs to be answered. More studies are needed to resolve this question, but on the basis of the current literature, the pathologies associated with survival of TBI seem to be as heterogeneous as the forms of TBI themselves. Considering the many shared pathological features that have been described, the changes could indicate a TBI dose effect, whereby a threshold that triggers neurodegenerative cascades can be reached as a result of one severe TBI or the cumulative effects of multiple mild TBI. Notably, whether exposure to repeated head impacts without a diagnosis of TBI — so-called subconcussive blows — can also trigger neurodegeneration remains to be determined.

While we await full and rigorous characterization of CTE, the current evidence does not support the widely accepted premise that it is exclusively a tauopathy that occurs only in people who have been exposed to repetitive mild TBI. Neither does the evidence support the idea that neurodegeneration after exposure to a single moderate or severe TBI is inevitably AD. Unquestionably, CTE encompasses a broader range of neuropathologies and outcomes after TBI of varying severity, and time will tell whether the condition is a distinct disease entity or is linked with other neurodegenerative processes such as AD. However, as CTE has

become embedded in the public consciousness and is fortified by the media, we are obliged to continue with the term. Meanwhile, the words of Corsellis from his original account of boxers over four decades ago are as relevant now as they were then: “most of the trenchant views that are expressed about the vulnerability, as well as the immunity, of the brain in [sport] are still based more on supposition than on fact”[15].

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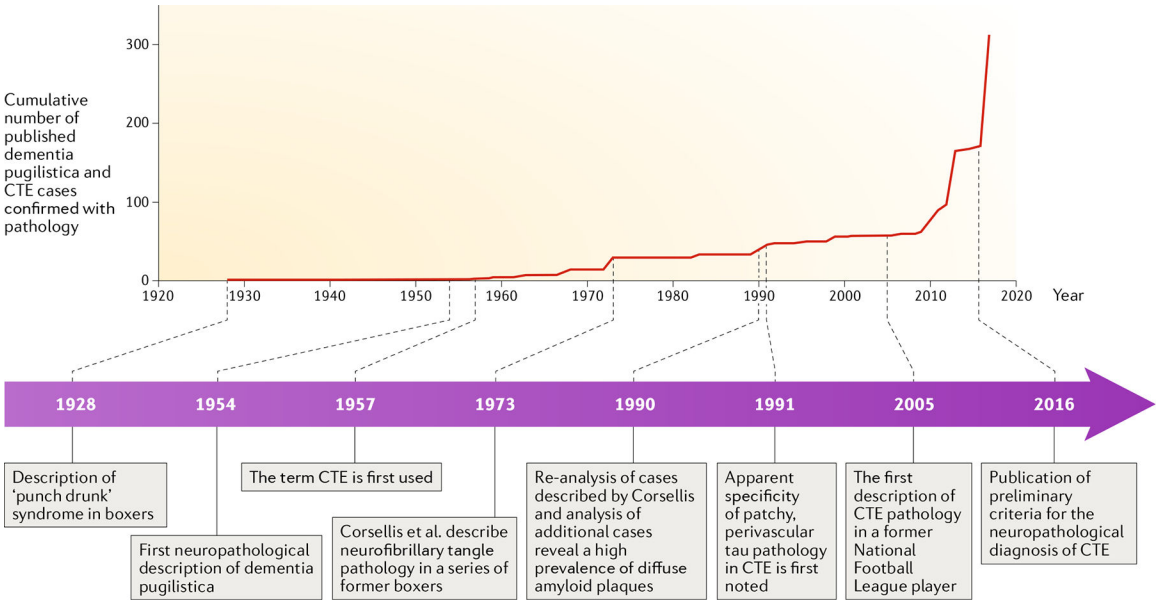

Fig. 1|. Historical timeline of developments and the cumulative number of published cases of dementia pugilistica and CTE.

The association between exposure to brain injury in boxing and the risk of neurodegenerative disease was first reported in 1928. Since the first description of the pathology in a former American National Football League player in 2005, a marked increase in case identification and reporting has been seen. Nevertheless, the cumulative number of unique chronic traumatic encephalopathy (CTE) cases reported is currently just over 300.

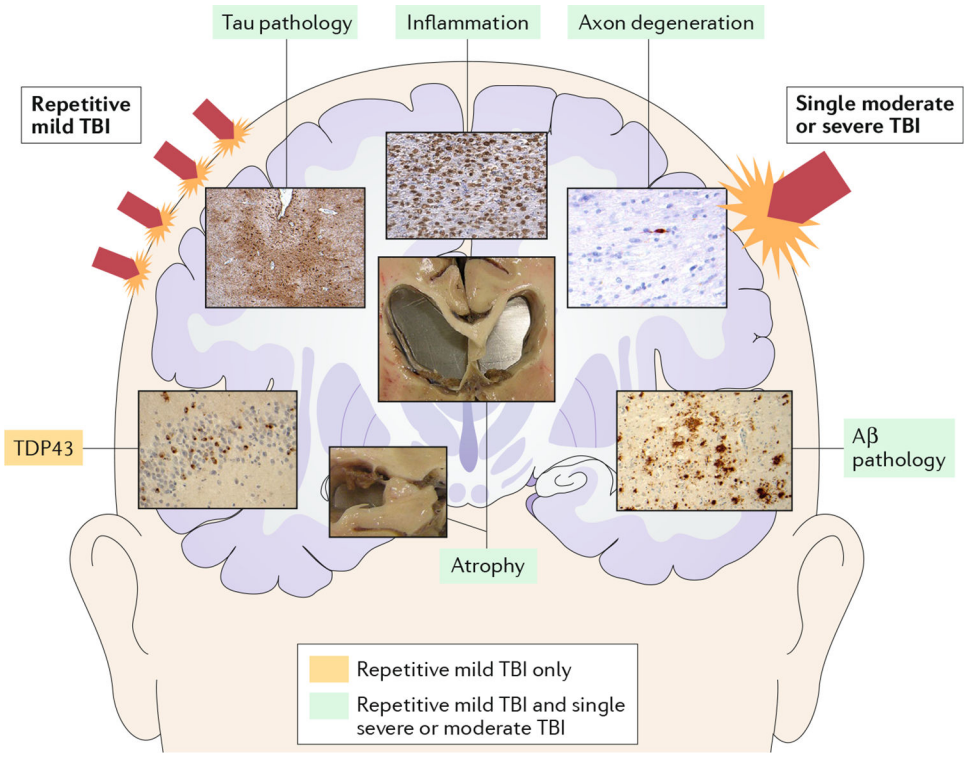

Fig. 2|. Neuropathologies identified as being associated with neurodegeneration after TBI.
For both repetitive mild traumatic brain injury (TBI) and single moderate or severe TBI, post-mortem neuropathology studies have identified tau and amyloid-β (Aβ) pathologies, brain atrophy, axonal degeneration and persistent neuroinflammation. However, thus far, 43 kDa transactive response (TAR) DNA-binding protein (TDP43) pathology has only been identified after repetitive mild TBI.