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Repetitive head trauma, chronic traumatic encephalopathy and tau: Challenges in translating from mice to men

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ABSTRACT

Chronic traumatic encephalopathy (CTE) is a neurological and psychiatric condition marked by preferential perivascular foci of neurofibrillary and glial tangles (composed of hyperphosphorylated-tau proteins) in the depths of the sulci. Recent retrospective case series published over the last decade on athletes and military personnel have added considerably to our clinical and histopathological knowledge of CTE. This has marked a vital turning point in the traumatic brain injury (TBI) field, raising public awareness of the potential long-term effects of mild and moderate repetitive TBI, which has been recognized as one of the major risk factors associated with CTE. Although these human studies have been informative, their retrospective design carries certain inherent limitations that should be cautiously interpreted. In particular, the current overriding issue in the CTE literature remains confusing in regard to appropriate definitions of terminology, variability in individual pathologies and the potential case selection bias in autopsy based studies. There are currently no epidemiological or prospective studies on CTE. Controlled preclinical studies in animals therefore provide an alternative means for specifically interrogating aspects of CTE pathogenesis. In this article, we review the current literature and discuss difficulties and challenges of developing in-vivo TBI experimental paradigms to explore the link between repetitive head trauma and tau-dependent changes. We provide our current opinion list of recommended features to consider for successfully modeling CTE in animals to better understand the pathobiology and develop therapeutics and diagnostics, and critical factors, which might influence outcome. We finally discuss the possible directions of future experimental research in the repetitive TBI/CTE field.

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1. Introduction

There is still much to be learned about the link between repeated traumatic brain injury (r-TBI) and the subsequent development of the degenerative neurologic disorder known as chronic traumatic encephalopathy (CTE). Since the late 1930s-TBI in professional boxers has been associated with chronic motor and neuropsychiatric symptoms, later referred as 'dementia pugilistica' (DP) (Millspaugh, 1937). With the appreciation that the pathology was not confined to boxing, the term CTE appeared in the medical literature in 1966 and is now the preferred term (Miller, 1966). However, CTE was not well known publically until the publication of two case reports identifying CTE in former NFL players (Omalu et al., 2005, 2006). Since then it has been the topic 'du jour' of sports and medicine for the last several years and now similar symptoms have been reported in a limited number of cases in military personnel exposed to improvised explosive devices (IED) and a history of participation in contact sports (Goldstein et al., 2012; McKee et al., 2013). We have little idea, however, of the risk factors involved in CTE following r-TBI, or of the basis of genetic predispositions that produce an overwhelming level of heterogeneity in susceptibility on top of the type/nature of the sustained TBI. Indeed, the features that constitute CTE as a distinct disease entity have yet to be clearly defined, due primarily to the confusing state of the current literature resulting from the highly selected nature of the cohorts, variability in individual pathologies described by different groups and also because there remains no validated definition or direct comparative analysis with other neurodegenerative diseases.

Some investigators have tried to subdivide CTE into two different categories, for example in a recent review article, Gardner et al., provides a critical review of the differences between the original descriptions of CTE referred to as "classic CTE" and the recent descriptions since 2005 referred to as: "modern CTE" (A. Gardner et al., 2014). However, the distinctions between these terms still remain unclear and the use of such terminologies may be potentially misleading. The diagnosis of CTE to date has been based exclusively on postmortem analysis. To date there have been two different neuropathological criteria, defined by Omalu and McKee. In this article we use the term 'CTE' based primarily on these postmortem diagnostic criteria.

The anatomical manifestation of CTE coming from post-mortem analyses include: a reduction in brain weight; atrophy of the frontal and temporal cortices and medial temporal lobe; enlarged ventricles; cavum septum pellucidum with septal fenestration; pallor of the substantia; atrophy of the olfactory bulbs, thalamus, mammillary bodies, brainstem and cerebellum (McKee et al., 2009, 2013). These physical manifestations are more pronounced as the disease progresses over time (McKee et al., 2013). Additionally, on a microscopic scale, the peculiar distribution within the brain of tau deposition is distinguishable from other tauopathies and has been proposed as a measure to diagnose and categorize the four different stages of progression of CTE (McKee et al., 2013). These neuropathological features include phosphorylated-tau (p-tau) immunoreactive neurofibrillary and astrocytic tangles in the frontal and temporal cortices (particularly around small cerebral vessels and at the depths of cerebral sulci); extensive p-tau immunoreactive neurofibrillary tangles in limbic regions, diencephalon and brainstem nuclei (McKee et al., 2013). Whether or not CTE is a true tauopathy (solely caused by tau) remains under debate as the pathology of TBI survivors could also be characterized as a disorder with multiple pathologies also referred as a "polypathology" (Faden and Loane, 2015; Faden et al., 2015; Smith et al., 2013). These chronic pathologies include the presence of amyloid plaques, TAR DNA-binding protein 43 (TDP-43), sustained neuroinflammation and axonal degeneration in the sub-cortical white matter brain regions (McKee et al., 2010, 2013).

In this article, we provide an overview of the current literature involving long-term pathophysiology of repetitive TBI and CTE with a focus on tau. We discuss the role of r-TBI in human CTE as well as the challenges of modeling CTE in laboratory animals. Finally, we will point out the benefits of the current preclinical models in understanding CTE.

The increased awareness of the serious dangers posed by exposures to repetitive mild TBI in sports, and the recent surge of funding have set the stage for increased research efforts. We anticipate that this will promisingly lead to breakthroughs in our current understanding of the pathogenesis of chronic head trauma or concussion, and the development of therapeutic strategies to mitigate their consequences

2. Repetitive mTBI and CTE

2.1. From repetitive TBI to CTE

At present there are no published epidemiological, longitudinal, cross-sectional or prospective studies involving CTE. Most of the published studies have been retrospective that examined patients at autopsy stages.

Nine decades ago, an established link between repetitive head injury and CTE (formerly referred to as punch-drunk syndrome or dementia pugilistica) was famously identified, stemming from the original reports by Martland in 1928 who presented the clinical details of a 38 year old professional boxer who fought from adolescence until his mid-twenties (Martland, 1928). During his career, the boxer suffered two concussions (with one lasting >1 h) and presented a stereotypical clinical picture of CTE 20 years after onset of symptoms. Although typically overlooked (Montenigro et al., 2014), this apparent link between brain injury and initiation of chronic degenerative injury had been introduced the previous year during a clinical study of 100 cases of concussion by Osnato and Giliberti (1927). The authors presented microscopic evidence of a constellation of neuropathological features later termed traumatic encephalopathy (Osnato, 1929), in a patient who suffered a TBI without fractures, contusion or laceration and died within 36 h post-injury. This patient demonstrated parenchymal degeneration situated around blood vessels and glial cells, accompanied by irregular staining of pyramidal cells in the cerebral cortex, possibly indicative of what might be the initiation process of the chronic progressive 'perivascular foci' seen in CTE following postmortem analyses many years after injury.

Many historical studies considered CTE exclusively as a disease of boxers and as such, several other investigators over subsequent years confirmed similar symptoms reported by Martland (1928) in retired professional boxers (Bowman and Blau, 1940; Brock, 1940; Critchley, 1957; Mawdsley and Ferguson, 1963; Millspaugh, 1937; Spillane, 1962). In the largest study of CTE cases by Roberts (1969), 250 retired boxers were investigated from a cohort of >16,000 boxers, some of who fought in an era of bare-knuckle championships where boxers received more repetitive head trauma exposures and little medical monitoring (Roberts, 1969). They confirmed neuropathological lesions of the nervous system in 37 cases (17%) and associated risk factors of CTE to include retirement after 28 years of age, participating in boxing for over a decade, and engaging in more than 150 fights.

Subsequent studies also confirmed that the neuropathological burden in these CTE cases appeared to correlate with the level of boxing

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