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Amyloid-beta and tau pathology following repetitive mild traumatic brain injury

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ABSTRACT

Neurodegenerative diseases are characterized by distinctive neuropathological alterations, including the cerebral accumulation of misfolded protein aggregates, neuroinflammation, synaptic dysfunction, and neuronal loss, along with behavioral impairments. Traumatic brain injury (TBI) is believed to be an important risk factor for certain neurodegenerative diseases, such as Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE). TBI represents a ubiquitous problem in the world and could play a major role in the pathogenesis and etiology of AD or CTE later in life. TBI events appear to trigger and exacerbate some of the pathological processes in these diseases, in particular, the formation and accumulation of misfolded protein aggregates composed of amyloid-beta (Aβ) and tau. Here, we describe the relationship between repetitive mild TBI and the development of Aβ and tau pathology in patients affected by AD or CTE on the basis of epidemiological and pathological studies in human cases, and a thorough overview of data obtained in experimental animal models. We also discuss the possibility that TBI may contribute to initiate the formation of misfolded oligomeric species that may subsequently spread the pathology through a prion-like process of seeding of protein misfolding.

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1. Introduction

The National Head Injury Foundation defines traumatic brain injury (TBI) as an "insult to the brain caused by an external force that may produce diminished or altered states of consciousness, which results in impaired cognitive abilities or physical functioning [1]". The World Health Organization estimates that 10 million people in the world are affected by TBI per year, specifically costing Americans $57 billion. TBI is the leading cause of death or disability noted in industrialized cities as well as in children and young adults. TBI reduces life expectancy by 7 years [2,3].

Mild TBI (mTBI) is acknowledged as head insults that cause a brief state of altered consciousness resulting ≤30 min of unconsciousness, yet most mTBIs do not result in loss of consciousness. The consequences of repetitive mild TBI (rmTBI) is a popular topic in research due to the fact that war veterans and contact sports

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athletes (i.e. American football, boxing, hockey, soccer, etc.) with TBI experiences are linked with a recently defined disease: chronic traumatic encephalopathy (CTE), formerly termed dementia pugilistica. Though the particular type of lesions resulting from mTBI are highly variable, various factors may play an important role in the consequences of the impact, including rotational acceleration and deceleration forces, fluidic pulses from the lateral ventricles generating shearing forces, blow location, among others [4]. Athletes and soldiers having CTE display an overlapping and broad range of abnormal behaviors emerging mid-life that ultimately result in psychological issues that lead to violence and/or suicide. Following a primary TBI insult a multitude of secondary mechanisms take effect causing cytopathogenesis and neurological changes within the brain, as indicated by an association with neurodegenerative diseases, cognitive struggles, seizures, sleep disorders, neuroendocrine disorders, and other complications [3]. These secondary mechanisms involve excitotoxicity, Ca^{2+} overload, mitochondrial dysfunction, reactive oxygen species, and inflammation. These cellular and biochemical alterations lead to synaptic dysfunction, axonal degeneration, and neuronal death; thereby, initiating cognitive impairments. Interestingly, autopsy brain samples from CTE-diagnosed athletes and military veterans and others affiliated with some form of TBI, from teen ages to 80's, display massive accumulation of misfolded protein aggregates, mainly composed of tau and amyloid-beta (Aβ).

Tau and Aβ inclusions are mostly known for their association with Alzheimer's disease (AD), which is the most common form of dementia affecting elderly individuals. Neurofibrillary tangles (NFTs) are formed by aggregates of hyper-phosphorylated tau protein (pTau). Tau is a microtubule associated protein that has six isoforms differing by 3R or 4R binding repeats. Tau plays an important role in axonal stabilization, neuronal development, and neuronal polarity. Aβ is a 38–43 amino acid peptide produced by the cleavage of the amyloid precursor protein (APP) by β- and γ-secretase. Under pathological conditions these proteins misfold and aggregate forming long fibrillar polymers, which bind amyloid dies (e.g Thioflavin S and Congo red), and have a high resistance to cellular proteolytic degradation [5–8].

In this article, we will discuss the intimate connection between rmTBI and AD/CTE by means of misfolding and aggregation of Tau and Aβ, analyzing epidemiological evidence, pathological and structural brain changes in patients, as well as data coming from experimental animal models.

2. Epidemiological evidence for a role of TBI in neurodegenerative diseases

Concussions and mTBI are some of the most common forms of neurological disabilities, estimating around 90% of all brain injuries recorded [4]. The Center for Disease Control and Prevention reported 300,000 mild TBI cases per year in contact sports, and about 122,000 children (ages 10–19) went to the ER annually for non-fatal brain injuries [9]. Studies involving American football players at various ages revealed that the absorbed head impacts per season rose in an exponential fashion: around 80 hits (ages 7–8); >240 hits (ages 9–12); >1000 hits (high school); and 420–2492 (college) [4,10,11]. The National Football League (NFL) reported an average concussion incidence of 131.2 ± 26.8 concussions per year – a rate of 0.41 concussions per game [12]. This demonstrates that an individual sport player suffers multiple damaging head blows and/or concussions that may produce accumulative damage over the years. However, the number and strength of impacts (i.e. sub-concussive versus concussive) required to lead to AD and CTE-associated pathology remains to be elucidated.

Though epidemiological studies are contentious, one major finding in human rmTBI cases is that the onset and severity of CTE appears to correlate with the length of time engaged in contact sports/military service and number of traumatic injuries that occur [2,4,9,13,14,32,33]. A previous study stated that 17% of retired boxers developed CTE, yet prevalence of CTE might be underestimated possibly due to paucity of reporting or cognizance of even acquiring rmTBI [2,4,9,12,36]. Retired NFL players having three or more concussions were found to have a five-fold increase of developing mild cognitive impairment – a stage that can evolve into AD or other forms of dementia [13]. In addition, 68 out of 85 post-mortem individuals with a history of rmTBIs developed CTE pathology [2]. Although the brain has been hypothesized to have the ability to recover following rmTBI, brain scans performed on high school American football players showed that the current in-season players versus those in off-season demonstrated comparable brain damage [15].

3. Neuropathological abnormalities induced by TBI

CTE is seen primarily in contact sports athletes and military personnel, and the disease appears to be triggered by rmTBI and be mostly associated to the formation and accumulation of NFTs and occasionally Aβ deposition. CTE is a slow-progressing disease and even if the trauma activity is halted, the disease still proceeds long-term thereby suggesting that the multiple molecular pathways elicited by rmTBI have long-lasting effects. Although mild head impact exposure is heavily linked to the development of neurodegenerative diseases, additional factors that may contribute to the development of CTE after rmTBI may include: 1) age, a young brain may be plastic enough for recovery as compared to old brain; 2) extent, nature and timing of the trauma; 3) genetics, e.g. ApoE gene; and 4) other health-related factors. CTE is generally distinguishable from other tauopathies and AD because it consists of a unique distribution of pathological changes throughout the brain. Furthermore, tau accumulation is the predominant feature of CTE associated to rmTBI, while Aβ deposits are not very conspicuous, unless in more severe forms of TBI. Currently, a conclusive CTE diagnosis cannot be made until post-mortem. NFTs, neuropil threads, and astrocytic tangles form in an irregular distribution and heavy density in the frontal and temporal cortices. They have a proclivity to arrange near small blood vessels, ventricles, sub-pial tissues and are chiefly located at cortical layers II and III [2,4,9,14,16]. Despite these pathological differences in CTE and AD, the tau isoforms that are hyper-phosphorylated remain identical between CTE and AD. It is still unclear the mechanism and signaling pathways implicated in NFT formation in CTE and what the role of this deposition plays in CTE-specific behavior.

Aβ is a hallmark of all AD cases, but only found in 30% of post-mortem acute TBI cases and 40–45% of CTE cases albeit with inconsistent deposits of diffuse, neuritic, or vascular plaques. Unlike AD, where Aβ plaques take decades to form, aggregation and deposition of Aβ is accelerated after an acute TBI event, appearing even in a span of hours [1–3,17–22]. A recent study analyzing 114 deceased athletes and veterans with CTE revealed Aβ accumulation increasing 2.7-fold for every decade in age for 52% of the subjects. In addition, CTE patients with Aβ had a trending for greater number of concussions reported, elevated CTE stage prognosis, and higher frequency of dementia than CTE subjects without Aβ [16]. The mechanism by which TBI promotes Aβ accumulation is unknown, but it has been suggested that rmTBI causes some type of axonal injury, which could disrupt axonal transport, leading to swollen axonal bulbs causing an accretion and co-accumulation of APP, β-secretase, and γ-secretase, thus a favorable environment for generating toxic Aβ from the swollen bulb and into the brain parenchyma [1,17,18,23]. Taken together, the presence of Aβ

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