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Injury Cascades in TBI- Related Neurodegeneration

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Abstract

Traumatic brain injury (TBI) is a widely-recognized risk factor for neurodegenerative disease. The purpose of this review is to provide an update on the state of the science related to injury cascades in TBI-related neurodegeneration. Acute and chronic pathological outcomes of TBI are similar to those seen in several neurodegenerative conditions, suggesting common linking pathways. Initial research described severe TBI patients with postmortem identification of abnormal proteins, such as amyloid deposits. History of mild TBI (mTBI) is less consistently associated with heightened risk of neurodegenerative outcomes, but specific populations with complicated medical histories and comorbidities may be more susceptible. Our understanding of a pathological signature associated with repetitive mTBI and/or subclinical brain trauma advanced significantly over the past decade, and is now commonly referred to as chronic traumatic encephalopathy. We discuss hypotheses linking TBI to neurodegenerative disease, and the importance of considering factors like injury severity, timing of injury (early life versus older age), injury frequency, and repetitive subclinical brain trauma when extrapolating results from current literature to certain populations. We describe the challenges to obtaining the data necessary for accurate epidemiological research and determination of true risk magnitude, and note the importance of developing treatment-based approaches to risk mitigation.

Introduction

Traumatic brain injury (TBI) and neurodegenerative disease are both international public health concerns. Heightened research efforts investigating links between these two conditions indicate TBI may elevate risk of developing neurodegenerative pathology by a variety of potential mechanisms. Harrison Martland first described poor long-term outcome specific to repetitive TBI mechanisms as “punch drunk” syndrome in 1928, later termed dementia pugilistica by Millspaugh in 1937 and “chronic progressive traumatic encephalopathy of boxers” by Critchley in 1957[1–3]. Chronic traumatic encephalopathy (CTE) is now a widely-recognized term among the public that was popularized over the past decade because of evidence suggesting athletes and military personnel exposed to repetitive

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brain trauma are at risk of the neurodegenerative pathology [4,5]. Studies also identify TBI as a possible environmental risk factor for more common degenerative diseases such as Alzheimer's disease (AD). Overlapping neuropathological outcomes between TBI and neurodegenerative disorders lend support to this association, though a great deal remains unknown. Here we note population and injury severity-specific considerations, and we briefly review hypothesized mechanisms, epidemiological studies describing diagnosed neurodegenerative disease and dementia after TBI exposure, and future research avenues.

TBI Severity and At-Risk Populations

TBI is described along a continuum from mild to moderate to severe based on gross neurological assessment and neuroimaging findings. Many consider "concussion" synonymous with mild TBI (mTBI). Recent concerns have emerged about repetitive subclinical brain trauma (RSBT), or forces transmitted to the brain that do not cross a threshold of observable or measurable functional changes but still likely result in shear-strain of axons. This is likely due to findings that repetitive trauma in certain sports (American football, ice hockey, and others) and soldiers has manifested as CTE or structural brain changes that do not necessarily correlate with a significant, documented concussion history. Civilians are at risk of single-event TBI of all severities via mechanisms such as motor vehicle accidents, assault, or falls, while certain collision sport athletes and military personnel are uniquely exposed to RSBT as well as more frequent mTBI. The degree to which findings from acute, severe TBI patients directly apply to those with extensive RSBT or multiple mTBI, and vice versa, is unclear, but such data likely identify candidate mechanisms underlying the relationships to later-life neurodegenerative disease.

Acute Pathophysiological Effects of Single-Event TBI

TBI results in diffuse axonal injury characterized by mechanical deformation of axons and subsequent indiscriminate glutamate release, spreading depolarization, and altered neuronal metabolism[6]. Dysregulated axonal transport systems lead to axonal swelling that may result in deprivation of necessary proteins at axon terminals and, ultimately, focal nerve disconnection (i.e. "secondary axotomy") or reduced elasticity[7]. Excess amount of proteins associated with TBI, beta-amyloid (Aβ) and phosphorylated tau (pTau), are implicated in many neurodegenerative diseases. Johnson et al. (2013) and Washington et al. (2016) review axonal and cellular polypathologies following TBI in greater detail[8,9].

Human TBI studies indicate that damaged axons "can serve as a large reservoir" of amyloid precursor protein (APP) and Aβ[10]. APP levels in the temporal cortex increase within hours after severe TBI in humans and localize to axonal swellings, neurites, and cell bodies in the absence of acute neurofibrillar pathology[11]. APP upregulation and accumulation is an established marker of diffuse axonal injury in TBI, significantly increasing risk for neurotoxic levels of Aβ[12,13]. Roberts and colleagues indicated approximately 30% of severe TBI patients test positive for Aβ plaques, and a significant effect of age such that incidence was 20% in those younger than 50 and 60% in patients between 51 and 60[14]. Studies also show significantly higher incidence of intracellular and intra-axonal accumulation of non-

plaque Aβ[11,15]. Similar results are noted in animal studies using fluid percussion and controlled cortical impact injury models[16–21].

The shear-strain force from TBI may result in hyperphosphorylation, misfolding, and accumulation of tau, which disrupts axonal transport systems. Presence of aggregated pTau as neurofibrillary tangles (NFTs) acutely after a single TBI is not as common as Aβ, but the distribution of tau pathology appears unique to TBI etiology. Uryu et al. examined brain tissue from 18 cases following single incident fatal TBI and found far less prevalence of pTau relative to APP accumulation within axons[22]. A more recent study compared NFT deposition in patients diagnosed with only a single TBI (with 1–47 years' survival) and found no difference in prevalence compared to an age-matched control group. However, the TBI group displayed NFTs more frequently when limiting analyses to subjects 60 years or younger. Deposition of age-related NFTs or tau deposition does not occur commonly in subjects below 60 years. The TBI group also had a unique distribution of NFT depositions in the cortical layers – clustering at depths of cortical sulci, compared to controls exhibiting NFTs predominantly in entorhinal cortex and the hippocampus, considered mostly consistent with normal aging[23]. Cortical NFTs are not widely seen with normal aging, but with clinically manifest Alzheimer's disease.

Hypotheses Linking TBI to Progressive Neurodegenerative Disease

Mechanisms driving the potential neurodegenerative effects of acute TBI, multiple mTBI, or RSBT are poorly understood. Proposed hypotheses include decreased cognitive reserve, chronic inflammation, chronic microglia activation, acute upregulation of APP and subsequent AD-like cascades, and slow degeneration of axonal connections due to altered protein degradation processes. The widespread effects of TBI on neuronal homeostasis and regulatory functions suggests one or many of these hypotheses may drive chronic dysfunction even in the absence of subsequent or repetitive forces transmitted to the brain.

The cognitive reserve hypothesis holds that the effects of TBI modify the "normal aging" trajectory for the affected individual, and multiple injuries may have synergistic negative effects that amplify or accelerate the risk of crossing a threshold for dementia diagnosis. Neuropathologically, acute neuroinflammation after TBI is associated with cytokine release and persistent microglia activation, evidenced by reactive microglia found post-mortem months to years after a single TBI[24–27]. Johnson and colleagues found reactive microglia present in 28% of brains examined over a year following a single TBI, which supports previous data indicating chronic inflammation and microglia activation up to 17 years after TBI in areas distal to the trauma locus[25,28].

As previously mentioned, acute TBI pathology can include Aβ and tau deposition. The normally functioning brain has mechanisms for protein degradation and removal. The ubiquitin-proteasome pathway, for example, is an intracellular mechanism that regulates degradation of both normal and abnormal proteins, and promotes normal cell growth and metabolism. This pathway may be impaired due to chronic inflammation following TBI, resulting in inability to clear proteins such as Aβ and pTau efficiently[29]. The combination of abnormal protein deposition and reduced degradation and clearance abilities suggest

plausible mechanisms linking single-event moderate to severe TBI to neurodegenerative processes.

Repetitive Brain Trauma and Neurodegeneration

Athletes participating in high frequency collision sports and certain military personnel are exposed to RSBT and potentially multiple mTBI[30]. CTE is the primary neurodegenerative tauopathy associated with RSBT and multiple mTBI history, though other proteomic molecules such as Aβ and TAR DNA-binding protein 43 (TDP-43) are also frequently observed. Recently published pathological criteria defined pTau aggregates in neurons, astrocytes, and cell processes around small vessels in cluster patterns at the depths of cortical sulci as the pathognomonic sign of CTE[31]. Continuous tau deposition in the cortical lamina differentiated AD from CTE, as does the absence, in CTE, of NFT deposition in other parts of the cortex and limbic system, particularly in milder cases of CTE. However, data show that up to 37% of individuals diagnosed with CTE pathology also met criteria for comorbid neurodegenerative pathology including AD, Lewy Body Disease, and frontotemporal lobar degeneration[5], largely in older subjects, CTE has been identified almost exclusively in individuals with a history of repetitive brain trauma, though some recent findings raise questions of whether such exposure is necessary[32,33]. Lack of prospective longitudinal studies or validated in vivo diagnostic markers, and current sample biases significantly limit accurate determination of CTE incidence and prevalence. Literature to date has not described CTE as an outcome of single-event TBI.

Absence of premortem CTE diagnostic markers complicates attribution of structural and functional changes seen in individuals with exposure to repetitive brain trauma, and thus, definitive diagnosis. Coughlin and colleagues found prolonged neuroinflammation in former National Football League (NFL) players associated with hippocampal atrophy as well as evidence of activated microglia years after retirement from sport[34], like previously described outcomes after single-event TBI. Although early case studies using positron emission tomography (PET) revealed uptake of tau-binding ligands in retired NFL players with retention distribution inconsistently characteristic of expected CTE patterns[35,36], more recent reports do show a pattern consistent with the pathological distribution associated with CTE. Increased cortical thinning, enlarged ventricles, subcortical atrophy, and diffuse white matter abnormalities have all been reported in retired NFL athletes[37–39]. Blood and cerebrospinal fluid (CSF) markers of central nervous system (CNS) injury may also provide insight to pathophysiological outcomes of RSBT and multiple mTBI. A recent study found a higher number of tau-positive exosomes in former American football athletes compared to retired non-collision sport athletes[40]. Alosco et al. reported a weak correlation between head impact exposure and plasma total tau levels, but no relationship with clinical outcomes[41]. Other studies demonstrated evidence of several markers of acute axonal injury following repetitive impacts sustained during a boxing match, but no differences between boxers and controls after three months of rest except for neurofilament light protein levels[42].

Risk of Dementia and Neurodegeneration Following TBI

Interpreting studies describing risk of dementia or neurodegenerative disease following TBI requires attention to time since injury (e.g. remote TBI history versus TBI in older adults), injury severity, and single-event versus repetitive injury (multiple mTBI and/or RSBT). There appears to be a weak statistical association between remote mTBI with loss of consciousness and incident dementia, on the order of 1.5 to 2.0-fold increased risk[43,44], with some evidence suggesting mTBI is a weaker predictor than many other neurobiological and psychosocial risk factors[45]. Other studies, however, have found no association[46,47]. Crane and colleagues found no association between remote mTBI and dementia or AD pathology, but reported a specific heightened risk of Lewy body pathology[48]. Mayeux et al. also found no association between TBI history and AD diagnosis, but reported a two-fold higher risk in individuals with apolipoprotein epsilon-4 (ApoE-ε4) and a ten-fold increased risk in those with *both* history of TBI and ApoE-ε4, raising the possibility of synergistic effects of TBI and genetic predisposition for neurodegenerative disease[49,50].

Data are similar in studies of older adults sustaining a TBI, with reported elevated risks ranging from 1.3 to 3.0 times greater likelihood of subsequent dementia diagnosis[51,52] and even higher risk in older individuals with the ApoE-ε4 genotype[53]. Gardner and colleagues assessed risk for dementia following TBI in older adults (minimum age 55) compared to older adults sustaining an orthopedic injury without brain trauma. They found that moderate to severe TBI was associated with increased dementia risk across all age groups, and mTBI was a significant predictor in older subjects only (65 and older)[54]. Thus, consideration of injury age, severity, and genetic interactions may be important for determining risk of neurodegenerative disease following TBI.

Studies of repetitive brain trauma associated with collision sport participation have shown inconsistent risks of later-life neurodegenerative disease or dementia. Lehman et al. found retired NFL players were at lower overall risk of mortality compared to age-matched controls, but had a three-fold increased risk of having either AD or amyotrophic lateral sclerosis (ALS) at death[55]. Two recent Mayo Clinic studies found no association between high school football participation and subsequent risk of dementia, Parkinson's disease (PD), or ALS, suggesting that risk was related to the degree of brain trauma exposure and length of playing career[56,57]. Like outcomes reported in single-event TBI studies, Jordan and colleagues described an interaction of genetics and brain trauma exposure such that the ApoE-ε4 genotype was associated with worse outcome in boxers with a high amount of exposure[58]. Maroon et al. systematically reviewed the initial 153 case reports of CTE and found no relationship between CTE and age of death or ApoE allele type, and concluded significant questions remain regarding the popularized belief of "widespread existence of CTE in contact sports[59]." Incidence, prevalence, and risk factors for CTE are currently unknown due to absence of longitudinal studies of representative populations; the clear majority of brains analyzed from subjects suffering multiple recurrent TBI were symptomatic before death and came to autopsy because of their clinical symptoms.

Challenges and Future Directions

Repetitive brain trauma research poses significant difficulties. Precise quantitative data is difficult to get in football and other collision sports, as well as military combat settings. Mechanistic differences between direct impacts seen in collision sports versus blast wave forces, and blast wave forces plus collision injury, in combat must also be studied. For example, a recent report from Shively and colleagues described potentially distinct pathological signatures associated with chronic blast exposure--specifically, astroglial scarring in the subpial glial plate, cortical blood vessels, grey-white matter junctions, and periventricular regions[60]. These findings were absent in cases of individuals with exposure to a single-event TBI, though a previous investigation from Goldstein et al. reported evidence of widespread astrocytosis in mice exposed to a single blast injury[61].

Co-occurring posttraumatic stress disorder (PTSD) is frequently a confounding issue in military settings, and retired collision sport athletes often have comorbid neurobiological and psychosocial conditions complicating the appraisal and attribution of cognitive, mood, and behavioral difficulties experienced after retirement[62]. Future research efforts must utilize prospective, longitudinal, and epidemiological designs for determining incidence and prevalence of CTE and other neurodegenerative diseases in populations at risk for TBI and/or RSBT relative to the general population. Advanced neuroimaging (e.g. PET[63]) and physiological biomarkers (e.g. CSF, serum, and plasma concentrations of CNS injury-related proteins) coupled with comprehensive neuropsychological evaluations will assist in defining clinical signatures of CTE and possible phenotypic subtypes. Family-based and case-control genetic studies may elucidate gene-environment interactions and identify individuals at higher risk of adverse outcome following TBI both acutely and chronically.

Lastly, and perhaps most importantly, treatment modalities must be studied targeting not only aggregation and propagation of neurodegenerative proteins such as tau and Aβ[16,64], but also modifiable risk factors believed to contribute to disease progression and overall quality of life, such as cardiovascular health, sleep disorders, psychiatric difficulties, and substance use, among others[62]. Models of the time course of AD pathology indicate that amyloid alteration precedes tau abnormalities by years, and that ongoing, chronic deposition processes may be occurring for a decade or more before observed evidence of cognitive or functional changes. Thus, it may be important to consider TBI as a risk factor for neuropathological outcomes separately from clinical outcomes (i.e. dementia), while also recognizing the role of prophylactic interventions that may prevent, delay, or slow formation of pathologic protein aggregates; and slow progression of disease through preservation or enhancement of neural structure and cognitive reserve.

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