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Post-traumatic neurodegeneration and chronic traumatic encephalopathy

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity around the world. Concussive and subconcussive forms of closed-head injury due to impact or blast neurotrauma represent the most common types of TBI in civilian and military settings. It is becoming increasingly evident that TBI can lead to persistent, long-term debilitating effects, and in some cases, progressive neurodegeneration and chronic traumatic encephalopathy (CTE). The epidemiological literature suggests that a single moderate-to-severe TBI may be associated with accelerated neurodegeneration and increased risk of Alzheimer's disease, Parkinson's disease, or motor neuron disease. However, the pathologic phenotype of these post-traumatic neurodegenerations is largely unknown and there may be pathobiological differences between post-traumatic disease and the corresponding sporadic disorder. By contrast, the pathology of CTE is increasingly well known and is characterized by a distinctive pattern of progressive brain atrophy and accumulation of hyperphosphorylated tau neurofibrillary and glial tangles, dystrophic neurites, 43 kDa TAR DNA-binding protein (TDP-43) neuronal and glial aggregates, microvasculopathy, myelinated axonopathy, neuroinflammation, and white matter degeneration. Clinically, CTE is associated with behavioral changes, executive dysfunction, memory deficits, and cognitive impairments that begin insidiously and most often progress slowly over decades. Although research on the long-term effects of TBI is advancing quickly, the incidence and prevalence of post-traumatic neurodegeneration and CTE are unknown. Critical knowledge gaps include elucidation of pathogenic mechanisms, identification of genetic risk factors, and clarification of relevant variables—including age at exposure to trauma, history of prior and subsequent head trauma, substance use, gender, stress, and comorbidities—all of which may contribute to risk profiles and the development of post-traumatic neurodegeneration and CTE. This article is part of a Special Issue entitled 'Traumatic Brain Injury'.

1. Introduction

1.1. Acute mild TBI

1.1.1. Concussive and subconcussive injury

Concussive and subconcussive injuries are thought to be produced by rapid acceleration and deceleration of the head (Meaney et al., 1995). Rapid linear or angular acceleration, deceleration or rotational forces cause the brain to deform, stretching individual neurons, glial cells and blood vessels and altering membrane permeability. Although

Abbreviations: TDP-43, 43 kDa TAR DNA-binding protein; AD, Alzheimer's disease; APOE ε4, apolipoprotein ε4; Aβ, beta-amyloid; CSF, cerebrospinal fluid; CTE, chronic traumatic encephalopathy; p-tau, hyperphosphorylated tau; mTBI, mild traumatic brain injury; NFTs, neurofibrillary tangles; PHF-tau, paired helical filament-tau; PET, positron emission tomography; PCS, post-concussion syndrome; TBI, traumatic brain injury.

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all cell compartments are affected by the injury, blood vessels and axons are especially vulnerable as they often extend long distances within the nervous system. In addition to structural deformation, traumatic acceleration–deceleration forces produce a rapid influx of calcium, efflux of potassium, release of neurotransmitters, and alterations in the function of cellular sodium–potassium ($Na+–K+$) pumps. These trauma-induced alterations in neuronal homeostasis result in large increases in glucose metabolism and are collectively referred to as the "neurometabolic cascade of concussion" (Giza and Hovda, 2001, 2014). Post-concussive hypermetabolism in the setting of decreased cerebral blood flow produces a disparity between glucose supply and demand or a cellular energy crisis (Giza and Hovda, 2001). Pathological studies show that multifocal axonal injury, microhemorrhage, loss of microvascular integrity, and neuroinflammation occur after concussion (Blumbergs et al., 1994; McKee et al., 2014; Oppenheimer, 1968). The astrocytosis is most severe in the cerebral white matter and brainstem white matter tracts and clusters of activated microglia are most prominent in the white matter around small vessels. Perivascular hemosiderin, hematoidin-laden macrophages and vascular inflammation may also be present after concussion, indicating microvascular damage and breach of the blood–brain barrier. In addition, focal perivascular accumulations of hyperphosphorylated tau (p-tau) and hyperphosphorylated TDP-43 (p-TDP43) occasionally occur after concussive injury (McKee et al., 2013, 2014).

The severity of the axonal injury and microvasculopathy generally parallel the severity of the TBI, with mild injury producing only microscopic axonal damage and rare microhemorrhages, and moderate to severe TBI producing more severe axonal injury with grossly visible petechial hemorrhages. The degree of axonal injury after traumatic impact may also vary with the direction of the head impact rotation, as experimental studies in gyrencephalic piglets demonstrate greater behavioral abnormalities and more persistent axonal injury in piglets exposed to sagittal versus axial rotational injury (Sullivan et al., 2013). The axonal injury produced by mild TBI (mTBI) is multifocal, with a tendency to be most severe in the corpus callosum, fornix, parasagittal white matter and cerebellum, and within these areas, more pronounced around small blood vessels (McKee et al., 2014).

These axonal changes likely contribute to the severity of symptoms after mTBI and are major contributors to the development of post-concussion syndrome (PCS). Acceleration–deceleration injury also causes tau protein, normally associated with microtubules in axons, to become abnormally phosphorylated, misfolded, aggregated and cleaved, all of which generate neurotoxic tau peptide fragments (Amadoro et al., 2006; Chen et al., 2010; Kanaan et al., 2011; Khlistunova et al., 2006; McKee et al., 2013; Zilka et al., 2006). It is not clear how these acute alterations develop into a progressive neurodegeneration after repeated injury in some individuals, however traumatically-induced microvasculopathy with breach of the blood brain barrier and release of normally excluded systemic proteins, such as proinflammatory cytokines or other factors may play a critical role. In addition, recent evidence indicates that a brain-wide network of paravascular channels, the "glymphatic" pathway, facilitates the clearance of interstitial solutes, including tau and beta amyloid (Aβ), from the brain. Experimentally in mice after acute TBI, the glymphatic pathway is functionally impaired, an impairment that persists for one month post injury and enhances the development of neurofibrillary pathology and neurodegeneration in post-traumatic rodent brain. Chronic impairment of glymphatic pathway function after repetitive TBI may be a key factor promoting tau aggregation and the onset of neurodegeneration (Iliff et al., 2014).

1.1.2. Blast injury

Blast injuries resulting from improvised explosive devices have become an increasingly important form of TBI in civilian and military populations. Recent estimates indicate that 10–20% of the 2.5 million U.S. military service members deployed to Iraq and Afghanistan are affected by TBI and the majority of these injuries are associated with blast exposure (The CDC et al., 2013). Individuals exposed to blast are susceptible to neurological injury with acute and long-term neuropsychiatric and cognitive consequences. Military personnel exposed to repetitive mTBI from explosive blast (Goldstein et al., 2012; McKee and Robinson, 2014; Omalu et al., 2011) show neuropathological changes of early stage CTE, axonopathy, microvascular damage, astrocytosis and activated microgliosis at autopsy (Goldstein et al., 2012). Clinical symptoms experienced after blast neurotrauma include progressive affective lability, irritability, distractibility, executive dysfunction, memory disturbances, and cognitive deficits. Four of the five veterans exposed to blast who showed changes of early stage CTE at autopsy were also diagnosed with posttraumatic stress disorder (PTSD) during life suggesting that PTSD and CTE might be biologically and pathologically interconnected (McKee and Robinson, 2014). The focal p-tau changes associated with blast neurotrauma share features of early CTE reported in young American football and soccer players, boxers, headbangers and others (Geddes et al., 1999; Goldstein et al., 2012; McKee et al., 2013, 2014). However, pathologies associated with blast exposure other than tau accumulation, including axonal injury and microvascular damage, most likely are important contributors to the clinical and behavioral abnormalities observed after blast injury. It is worth noting that laboratory mice exposed to a single experimental blast also demonstrate brain pathology, physiologic and functional changes very similar to those found after human blast injury—including myelinated axonopathy, focal microvasculopathy, neuroinflammation, neuronal loss, phosphorylated tau proteinopathy, electrophysiological abnormalities, behavioral impairments, and cognitive deficits (Goldstein et al., 2012). An independent replication study reported brain tau proteinopathy that persisted for at least one month after exposing mice to a single blast (Huber et al., 2013).

Blast injuries represent a wide range of heterogeneous injuries and are often complicated by other types of TBI, including closed-head impact injury (Nakagawa et al., 2011). The occurrence of microscopic neuropathology related to military blast exposure was first reported in deceased World War I infantry soldiers by Sir Frederick Mott (Mott, 1916, 1919). While blast-induced brain pathology has been repeatedly reported in humans and experimental animals, the origins of these injuries are only recently beginning to be understood (Goldstein et al., 2014). Kinematic analysis of high-speed videographic records obtained in a military-relevant blast neurotrauma mouse model has shown that blast winds with velocities of more than 330 miles/h—greater than the most intense wind gust ever recorded on earth—produce rapidly oscillating inertial forces on the head that induce injurious shearing forces in the brain (Goldstein et al., 2012). An important point is that blast winds, not blast waves, are responsible for the resulting cerebral injury, whereas the acoustic blast wave produces little deformation of brain tissue as a consequence of rapid shockwave pressure equilibration (Goldstein et al., 2012). Blast injuries may also produce diffuse or focal hemorrhage and edema as blood vessels and brain tissue rapidly contract and expand several times within the fraction of a second following transit of the blast shock wave. Some of the traumatic effects of blast exposure can be mitigated by immobilizing the head during blast exposure.

1.1.3. Juvenile head trauma syndrome and second impact syndrome

In children and young adults, minor brain trauma can occasionally produce catastrophic, often fatal, cerebral edema and coma. If the neurological deterioration occurs after a single TBI, it is referred to as juvenile head trauma syndrome (McQuillen et al., 1988). The neurological collapse may be immediate or delayed, occurring after a "lucid interval". Juvenile head trauma syndrome is thought to represent rapid vasodilation and redistribution of blood into the brain parenchyma after impact injury, a process that may involve a functional age-related channelopathy. Some individuals with juvenile head trauma syndrome have a mutation in the calcium channel subunit gene (CACNA1A) associated with familial hemiplegic migraine (Kors et al., 2001). Occasionally, juvenile head trauma syndrome develops in a young athlete who experiences

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