Military-related traumatic brain injury and neurodegeneration

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Abstract

Mild traumatic brain injury (mTBI) includes concussion, subconcussion, and most exposures to explosive blast from improvised explosive devices. mTBI is the most common traumatic brain injury affecting military personnel; however, it is the most difficult to diagnose and the least well understood. It is also recognized that some mTBIs have persistent, and sometimes progressive, long-term debilitating effects. Increasing evidence suggests that a single traumatic brain injury can produce long-term gray and white matter atrophy, precipitate or accelerate age-related neurodegeneration, and increase the risk of developing Alzheimer's disease, Parkinson's disease, and motor neuron disease. In addition, repetitive mTBIs can provoke the development of a tauopathy, chronic traumatic encephalopathy. We found early changes of chronic traumatic encephalopathy in four young veterans of the Iraq and Afghanistan conflict who were exposed to explosive blast and in another young veteran who was repetitively concussed. Four of the five veterans with early-stage chronic traumatic encephalopathy were also diagnosed with posttraumatic stress disorder. Advanced chronic traumatic encephalopathy has been found in veterans who experienced repetitive neurotrauma while in service and in others who were accomplished athletes. Clinically, chronic traumatic encephalopathy is associated with behavioral changes, executive dysfunction, memory loss, and cognitive impairments that begin insidiously and progress slowly over decades. Pathologically, chronic traumatic encephalopathy produces atrophy of the frontal and temporal lobes, thalamus, and hypothalamus; septal abnormalities; and abnormal deposits of hyperphosphorylated tau as neurofibrillary tangles and disordered neurites throughout the brain. The incidence and prevalence of chronic traumatic encephalopathy and the genetic risk factors critical to its development are currently unknown. Chronic traumatic encephalopathy has clinical and pathological features that overlap with postconcussion syndrome and posttraumatic stress disorder, suggesting that the three disorders might share some biological underpinnings.

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1. Introduction

In military settings, most traumatic brain injuries (TBIs) are mild TBIs (mTBIs). For U.S. forces deployed to Afghanistan and Iraq in Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND), blast exposure is the leading cause of mTBI, although service members are also susceptible to concussions [1]. Estimates of the prevalence of mTBI among returning service members range from 15.2% to 22.8%, affecting as many as 320,000 troops [1–4]. Despite their frequency, the acute and long-term effects of mTBI have been a relatively unexplored area of medical inquiry until very recently. Undoubtedly, the "invisible" nature of mTBI, notably the lack of any external physical evidence of damage to the head or brain, has been a major factor contributing to the impression of inconsequentiality. However, there is accumulating evidence that some individuals develop persistent cognitive and behavioral changes after mild neurotrauma. In addition, the relative contributions of physical injury or psychic stress to chronic sequelae after mTBI remain a matter of debate– a discussion that began during World War I regarding the basis for "shell shock," and that continues today concerning the relative contributions of posttraumatic stress disorder (PTSD) and physical brain injury to persistent symptoms after mTBI.

The first large-scale evidence of military-related mTBI occurred in World War I (1914–1918) in association with the frequent use of high explosives in trench warfare. Service members who experienced high doses of explosive artillery fire sometimes developed shell shock or "commotio cerebri," a mysterious condition characterized by headache, amnesia, inability to concentrate, difficulty sleeping, depression, and suicidality [5–7]. At the time, it was unclear whether shell shock was a maladaptive, psychiatric condition related to the stresses of combat or whether the condition was caused by physical injury to the brain. Despite the lack of any pathological studies on the brains of individuals diagnosed with shell shock, wartime committees entreated with the responsibility to inquire into the entity declared the disorder to have psychiatric origins [7].

Shortly thereafter, Harrison Martland, a New Jersey pathologist, drew attention to a symptom complex that affected professional boxers, "Punch Drunk," a condition well known to boxing enthusiasts that appeared to result from repeated sublethal blows to the head [8]. Martland described unsteadiness of gait, mental confusion, and slowing of muscular movements occasionally combined with hesitancy in speech, tremors of the hands, and nodding of the head. Later, Winterstein summarized the psychiatric manifestations of approximately 50 professional boxers and noted impairment of intelligence, mental dullness, difficulty concentrating, paranoia, and garrulousness [9]. Johnson later added memory loss, dementia, rage reactions, and morbid jealousy to the clinical syndrome [10]. In the scattered, small case series of "dementia pugilistica" reported over the next half century, the condition

was variously referred to as "traumatic progressive encephalopathy" and later as "chronic traumatic encephalopathy" (CTE) to highlight the chronic and progressive nature of the disorder [11,12]. In 1973, Corsellis, Bruton, and Freeman-Browne detailed the neuropathological findings found in the brains of 15 retired boxers and correlated the pathological findings with retrospective clinical symptoms [13]. The authors noted gross neuropatho-logical changes of cerebral atrophy, enlargement of the lateral and third ventricles, thinning of the corpus callosum, cavum septum pellucidum with fenestrations, and cerebellar scarring. General cell stains and Von Braunmühl's silver stain were used to demonstrate neuronal loss in the cerebellar tonsils and substantia nigra, neurofibrillary degeneration of the substantia nigra and cerebral cortex, and senile plaques in approximately one quarter of the cases. The authors speculated that pathology in the limbic structures (such as the hippocampus, medial temporal lobe, and fornix) was responsible for impairments in learning and memory, that pathology in the substantia nigra accounted for the Parkinsonian features, and that pathology in the septal cortex for the abnormal rage reactions.

Studies of CTE in boxers were followed by reports of CTE in civilians exposed to repetitive brain trauma as a consequence of head-banging behaviors, physical abuse, and poorly controlled epilepsy (reviewed in [14]); other sports, including Omalu's seminal observations in American football players [15,16]; and in ice hockey, baseball, soccer, rugby, and professional wrestling [14,17,18]. CTE was also reported in a few Iraq and Afghanistan veterans whom experienced military-related blast TBI [17,19,20]. In addition, CTE has been reported in military veterans, many of who were also athletes, including former National Football League (NFL) players [17]. CTE has been reported in military veterans who saw combat in the Gulf War, Vietnam, World War II, and Iraq and Afghanistan. In this review, we summarize the acute and long-term effects of mTBI that have been reported in veterans and describe the experience over the past 6 years at the VA Boston Brain Bank with military service-related mTBI.

Understanding the effects of military-related mTBI presents additional challenges not encountered in studies of neurotrauma associated with play of sports. Unlike the relatively stereotyped features of brain trauma that occur during athletic participation, in which injury is dependent on the rules of engagement specific to the sport, military-related mTBI is acquired in widely heterogeneous ways, including athletics, recreational activities, physical training practices (e.g., combatives, boxing competitions, and ropes courses), falls, motor-vehicle accidents, and exposure to explosive blasts. Injury from explosive blasts varies depending on the strength of the explosive; whether the injury occurs in an open field, in, or near buildings; or in a motor vehicle. Military mTBI is also random and unpredictable, ranging from a single injury to many thousands of traumatic injuries over similar time periods depending on an individual's chance exposure to blasts and impacts.

1.1. Acute injury

1.1.1. Concussion, subconcussion—A concussion is a mTBI induced by an impulsive force transmitted to the head resulting from a direct or indirect impact to the head, face, neck, or elsewhere [21,22]. In the combat setting, most concussions occur as a result of blunt trauma associated with blasts from explosive devices, such as hitting the head against the

interior of a vehicle [23]. Symptoms from concussion and other forms of mTBI are usually self-limited and resolve spontaneously over a period of a few weeks, although 10–15% of individuals develop prolonged symptoms or postconcussive syndrome (PCS). Signs and symptoms of concussion and PCS include irritability, sleep disturbance, forgetfulness, anxiety, headaches, poor concentration, pain, and psychological distress [24]. Neuropsychological testing in PCS may reveal persistent, yet subtle, cognitive deficits, often in the executive domain [24]. Less severe impact injuries that do not produce overt neurological symptoms but are associated with subtle neuro-psychiatric deficits or changes in functional magnetic resonance imaging (fMRI) are referred to as "subconcussion" [25,26]. Concussion and subconcussion are produced by acceleration and deceleration forces on the brain that may be linear or rotational [27]. Rapid acceleration, deceleration, or rotational forces cause the brain to elongate and deform, stretching individual cells and blood vessels and altering membrane permeability. Although all cell compartments are affected by the injury, axons are especially vulnerable to shear injury given their relatively long length and high membrane-to-cytoplasma ratio. In addition to axonal damage, the integrity of the microvasculature is compromised, with disruption of the blood-brain barrier and focal cortical hypoperfusion [28]. Moreover, acceleration-deceleration forces produce rapid release of neurotransmitters, including glutamate, and alterations in sodium channels with subsequent ionic dysregulation [29], producing an influx of calcium and an efflux of potassium, acceleration of the cellular sodium-potassium (Na^+-K^+) pump to maintain membrane homeostasis, and large increases in glucose metabolism [30].

Pathological studies of concussion and PCS demonstrate microscopic evidence of multifocal traumatic axonal injury (TAI) [18,31] that is best visualized by amyloid precursor protein (APP) immunohistochemistry [32], often located around small blood vessels in the corpus callosum, fornix, subcortical U-fibers, and cerebellum [18]. In general, the severity of the multifocal axonal injury is parallel to the severity of the TBI. However, APP immunohistochemical identification of traumatic axonal swellings may significantly underestimate the overall magnitude of the axonal damage [33]. TAI affects multiple axonal populations, including large caliber myelinated and non-neuropathologically detected fine-caliber myelinated and unmyelinated fibers. There is evidence that fine-fiber unmyelinated axons are disproportionately vulnerable to traumatic injury and, as such, may be significant contributors to the morbidity associated with mTBI. There are currently no reliable neuro-pathological markers for unmyelinated fine-fiber damage; accordingly, it is likely that the total axonal damage associated with TAI is considerably more than what is detectable with conventional neuropathological methods [33]. In addition, concomitant with the break-down of the axon and myelin sheath, axon terminals also undergo neurodegenerative change and deafferentation. This axonal degeneration and deafferentation likely contribute significantly to the morbidity associated with TAI. Furthermore, deafferentation sets the stage for subsequent neuroplastic changes that may be adaptive or maladaptive. These neuroplastic responses to mild neuro-trauma have not been well studied in the human brain [34,35].

After concussion, there is pathological evidence of blood-brain barrier damage with microhemorrhage, astrocytosis, and perivascular clusters of activated microglia [18]. In addition, some cases of recent concussion and PCS show isolated focal perivascular accumulations of hyperphosphorylated tau (p-tau) as neurofibrillary tangles (NFTs) and

neurites as well as hemosiderin-laden macrophages. The finding of focal p-tau abnormalities in the brains of individuals with PCS in close proximity to focal axonal injury, microhemorrhage, astrocytosis, and perivascular microgliosis suggests that the development of p-tau pathology may be mechanistically linked to axonal injury, breach of the blood-brain barrier, and neuroinflammation [18]. Whether these acute pathologies are reversible and resolve over time is unknown. Because most patients with mTBI recover fully, it suggests that intrinsic mechanisms are generally able to repair low-level injury [33]. However, repetitive TAI superimposed on continuing, perhaps broadening, breach of the blood-brain barrier; disruption of sodium channels; ionic dysregulation; and metabolic irregularities might trigger a self-perpetuating, progressive neurodegenerative cascade in some individuals.

Concussion and subconcussive injury are associated with microstructural changes in the white matter and alterations in fiber tract integrity that are detectable with diffusion tensor imaging (DTI) and susceptibility weighted imaging but are not evident on conventional structural imaging studies such as computed tomography (CT) scan and magnetic resonance imaging (MRI). The significance of these asymptomatic subconcussive injuries is increasingly recognized in sports such as football, ice hockey, and soccer, in which accumulating evidence demonstrates microstructural changes in the white matter on DTI as well as abnormalities in functional MRI (fMRI) [26,36–40]. Similar changes recently have been demonstrated in asymptomatic military-related blast injury [37,41]. Bazarian and colleagues found a strong association between exposure to blast and reduced first percentile fractional anisotropy (FA) on DTI that was independent of symptoms of mTBI at the time of blast exposure. Because these asymptomatic mTBIs are difficult to assess, it is likely that DTI and fMRI will become useful tools to guide the prognosis and management of these injuries moving forward.

Our experience with repetitive concussive injury includes a 28-year-old male U.S. Marine veteran with two combat deployments. Similar to many other military personnel, his history was notable for multiple concussions that occurred as a civilian and in combat. His first concussion occurred at age 12 in a bicycle accident with temporary loss-of-consciousness (LOC) and posttraumatic amnesia (PTA). At age 17, he experienced a second concussion without LOC during football practice. At age 25, during his second military deployment, he experienced a third concussion with temporary alteration in mental status but no LOC, after which he was diagnosed with PTSD. Four months later at age 26, he sustained a fourth concussion with temporary LOC and PTA resulting from a motor vehicle-bicycle collision. He subsequently developed persistent anxiety, difficulty concentrating, word-finding difficulties, learning and memory impairment, reduced psychomotor speed, and exacerbation of PTSD symptoms. He died from a self-inflicted gunshot wound 2 years after his last concussion. Neuropathological analysis revealed multiple areas of p-tau immunoreactivity surrounding small blood vessels in the temporal cortex, consistent with the diagnosis of early-stage CTE, although the limited availability of tissue precluded any further histo-logical analysis.

1.1.2. Blast injury—Most military-related TBI comes from exposure to explosive blast; blast TBI accounts for approximately 60% of military-related TBI, of which 80% is mTBI

[3]. The physical effects of the blast depend on many factors, including the characteristics of the improvised explosive device (IED); the relationship of the individual with respect to the source of the blast, including the distance from the blast; whether the exposure occurred in an open environment or in an enclosed space such as a building or vehicle; and whether a solid structure is located between the individual and the device, because the reflection of blast pressure waves off of various surfaces can lead to multiple pressure waves impacting an individual from various directions for a prolonged period [42]. Blast injury is often further complicated by an accompanying concussive mTBI.

Blast injury is the result of the rapid transmission of an acoustic wave through the brain tissue and accompanying blast winds [20]. Many animal models of blast-induced injury exist, although the precise biomechanics of blast-related traumatic injury and its neuropathological consequences are the subject of debate [43,44]. In our experience with experimental single-blast injury in wild-type C57BL/6 mice [20], detailed kinematic analysis demonstrated that blast winds produce forces similar to multiple, severe concussive impacts occurring over microseconds. In addition, simultaneous intracerebral pressure recordings demonstrated that blast waves traversed the brain with minimal change. The blast wavefront transmissions were not associated with thoracovascular or hydrodynamic contributions; indeed, separation of the mouse head from the thorax did not significantly change the blast-induced intracerebral pressure amplitudes. Furthermore, head immobilization during blast prevented neurological sequelae, confirming that the effect was not triggered by blast waves but rather by inertial forces from blast wind (the "bobblehead effect").

Pathologically, blast injuries produce hemorrhage and edema as blood vessels and brain tissue rapidly contract and expand several times within a fraction of a second after a blast wind, damaging cerebral vasculature [45]. In the acute phases, blast injury may produce large intraparenchymal and subarachnoid hemorrhages [46–48]. Blast injury is also associated with pseudoaneurysm formation and the development of vasospasm. When severe, vasospasm can lead to cerebral ischemia and clinical deterioration that can be delayed as long as 30 days after initial blast exposure [49–51]. Lu and colleagues investigated the effects of relatively low-level single and repetitive primary blast injury in nonhuman primates [52]. Ultrastructural analysis and histopathology at 3 days and 1 month postinjury revealed microvascular degeneration and collapse with obliterated capillary lumens, hypertrophic astrocytic end-feet, vacuolated endothelial cytoplasm, and increased perivascular reticuloendothelial cells. Other changes included chromatolysis of cortical neurons, hippocampal pyramidal neurons, and Purkinje cells in the cerebellum; white matter damage; and increased astrocytic aquaporin-4, suggesting cerebral edema.

The number of neuropathological analyses of acute blast injury in humans are few. In the instances reported by Mott, there was mild brain edema, severe vascular congestion, variable amounts of extravasation of blood around small vessels, intraparenchymal and subarachnoid hemorrhage, and generalized chromatolysis of neurons [5,6]. Warden and colleagues described the neuroimaging findings in a service member exposed to a series of large explosions. Three months after exposure, the service member still experienced headache, occasional nausea, and eye twitching, but she was found to have a normal neurological

examination. Her MRI showed a resolving hematoma in the internal auditory canal and an area of hyperintensity in the cerebellum. In addition, there was abnormal FA in the cerebellar white matter on DTI [53]. Other investigators using DTI have demonstrated lower FA and higher radial diffusivity after blast injury [41,54], although the white matter abnormalities found in various studies tend to be heterogeneous and spatially diverse. Using [18 F]-fluorodeoxyglucose positron emission tomography imaging of cerebral glucose metabolism, Peskind and colleagues demonstrated regional brain hypometabolism in veterans with repetitive blast injury [55]. A recent study of Iraq and Afghanistan veterans with one or more blast/impact mTBIs found reduced FA in the corpus callosum; reduced macromolecular proton fraction values in white matter tracts and gray matter/white matter border regions; reduced glucose metabolism in the cerebral cortex; and higher scores on measures of PCS, PTSD, combat exposure, depression, sleep disturbance, and alcohol use. The neuroimaging metrics did not differ between participants with versus those without PTSD [56].

We examined the postmortem brains of four young military veterans ($n = 4$ males; ages 22–45 years; mean 32.0 years) with histories of known blast exposure ranging from 1 to several years before death and found evidence of myelinated fiber loss, axonal degeneration, microvascular degeneration, neuroinflammation, and early changes of CTE.

A 28-year-old male U.S. military Marine veteran who experienced several blast exposures during multiple tours in Iraq and Afghanistan subsequently developed severe behavioral abnormalities including poorly controlled anger, debilitating social isolation issues, difficulty with attention and concentration, aggressive tendencies, paranoia, difficulty sleeping, and depression. At age 25, he "snapped" and attempted suicide in Afghanistan. He was diagnosed with combat-related PTSD. At age 27, he was honorably discharged from the Marines. At age 28, during an early-morning incident in which he allegedly fired on police and other civilians, he was shot and killed. At autopsy, his brain weighed 1410 g and was remarkable for slight thinning of the posterior body of the corpus callosum and discoloration of frontal tracts in the cerebral peduncle. Microscopically, there was evidence of severe axonal loss with widespread axonal swellings and axon retraction bulbs, myelinopathy, astrocytosis, and foci of dystrophic calcification in the cerebral subcortical white matter, internal capsule, and cerebellar white matter. Myelinated fiber loss was particularly prominent in the frontal lobes and frontal tracts of the cerebral peduncle. A single focus of perivascular p-tau NFTs and neurites was found at the sulcal depths of the inferior parietal cortex consistent with Stage I/IV CTE (Fig. 1, case 1).

A 45-year-old male U.S. Army veteran with a single close-range IED blast exposure experienced a state of disorientation without LOC that persisted for 30 minutes after blast exposure. He subsequently developed headaches, irritability, difficulty sleeping and concentrating, and depression that continued until his death 2 years later from a ruptured giant basilar aneurysm. His medical history was notable for a concussion associated with a motor-vehicle accident at age 8 years. At autopsy, neuropathological analysis showed acute intrapontine hemorrhage and bilateral infarction in the posterior cerebral artery territories. Microscopic examination also revealed multiple areas of perivascular p-tau NFTs in the frontal, parietal, and temporal cortices with a predilection for sulcal depths and superficial

cortical layers diagnostic of CTE Stage II/IV. Myelinated fiber degeneration with axon retraction bulbs and axonal dystrophy was found, most prominently perivascularly, in areas well away from the areas of infarction. There were also perivascular clusters of activated microglia in the subcortical white matter [20] (Fig. 1, case 2).

A 34-year-old male U.S. Marine veteran without a history of previous concussive injury sustained two separate IED blast exposures 1 and 6 years before death. Both episodes resulted in LOC of indeterminate duration. He subsequently developed depression, short-term memory loss, word-finding difficulties, decreased concentration and attention, sleep disturbances, and executive function impairments. His neuropsychiatric symptoms persisted until death from aspiration pneumonia after ingestion of prescription analgesics. At postmortem examination, there was evidence of CTE Stage II/IV and widespread hypoxic-ischemic injury [20] (Fig. 1, case 3).

A 22-year-old male U.S. Marine veteran was exposed to a single close-range IED blast exposure 2 years before death. There was no LOC, but he reported headache, dizziness, and fatigue that persisted for 24 hours after the blast. He subsequently developed daily headaches, memory loss, depression, and decreased attention and concentration. In the year before his death, he became increasingly violent and verbally abusive with frequent outbursts of anger and aggression. He was diagnosed with PTSD 3 months before death from an intracerebral hemorrhage. His past history included 2 years of high school football and multiple concussions from altercations. At autopsy, there was an acute intraventricular hemorrhage with tonsillar herniation. There was also evidence of multifocal axonal injury and p-tau neuritic immunoreactivity consistent with CTE Stage I/IV. In the thalamus, multiple small- to medium-sized blood vessels showed prominent perivascular lymphocytic cuffing as well as foci of lymphocytes and hemosiderin-laden macrophages within the vascular walls. Focal dystrophic calcification was also found in the walls of scattered small blood vessels in the thalamus and subcortical white matter (Fig. 1, case 4).

A similar case involving a 27-year-old veteran who had been exposed to multiple mortar blasts and IEDs was reported by Omalu and colleagues [19]. The veteran had developed progressive cognitive impairment, impaired memory, behavioral and mood disorders, and alcohol abuse, and he was diagnosed with PTSD. He committed suicide approximately 8 months after his discharge. His brain at autopsy showed changes of CTE consisting of multifocal NFTs that were most prominent at the depths of sulci in the frontal cortex.

Of interest, two of the five veterans died from spontaneous intracerebral hemorrhage several years after exposure to explosive blast, one died secondary to rupture of a giant basilar aneurysm, and the other died of intraventricular hemorrhage. The unusual locations of the hemorrhages might be interpreted to suggest that vascular integrity was initially compromised by the blast exposure and that subsequent vascular degeneration led to basilar artery aneurysm formation in one individual and to focal vasculitis and small vessel rupture in the other. The findings of focal dystrophic calcification and lymphocytic and hemosiderin-laden macrophage infiltration in the walls of small thalamic vessels in one individual support the concept of trauma-associated vasculitis and vascular degeneration (Fig. 1, case 4).

The changes of CTE, axonal injury, and microvasculopathy found in the postmortem brains of blast-injured veterans are consistent with neuroimaging studies of blast-injured service members showing white matter abnormalities and cerebral glucose hypometabolism [52–56]. The pathological changes found after blast are also strikingly similar to the pathological findings found in young athletes exposed to sports-related impact injuries [20]. The histological parallels suggest that similar biomechanical mechanisms underlie concussion and blast-related neurotrauma [20]. Experimental blast neurotrauma mouse models using wild-type C57BL/6 mice provide additional evidence linking the two types of trauma [20,41]. Two weeks after wild-type mice were exposed to a single blast, neuropathological analysis demonstrated hy perphosphorylated tauopathy, myelinated axonopathy, micro-vasculopathy, astrocytosis, and microgliosis that in several ways recapitulated human CTE pathology. These neuropatho-logical changes were associated with hippocampal-dependent learning and memory deficits that persisted for at least 1 month and correlated with impaired axonal conduction, which also mirrors some of the clinical aspects of human blast mTBI [20]. Moreover, a recent study in C57BL/6 mice demonstrated acute elevations of p-tau and cleaved tau species after a single blast exposure; these elevations were significantly higher than levels in similarly anesthetized, sham-treated mice and persisted for at least 30 days after blast exposure [57].

1.2. Chronic effects of TBI

1.2.1. Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis—Moderate-to-severe TBI is associated with progressive atrophy of gray and white matter structures that may persist months to years after injury [58,59]. In addition, multiple studies support a link between single moderate-severe TBI and Alzheimer's disease (AD) [60,61], Parkinson's disease (PD) [62], and amyotrophic lateral sclerosis (ALS) [63,64]. In a meta-analysis of 15 case-control studies, males who had a single head injury associated with LOC had a 50% increased risk of AD dementia [60]. A longitudinal study involving World War II Navy veterans also demonstrated increased risk for AD in late life with increasing TBI severity [61]. Veterans with severe TBI were 4 times more likely to have AD, whereas veterans with moderate TBI were twice as likely to have AD in late life compared with controls [61]. No increased risk was found for veterans who had a mild TBI. Some studies have also suggested that TBI is associated with an earlier onset of AD [65]. An analysis of 1283 TBI survivors found that the time to onset of AD was significantly reduced in those who sustained a TBI compared to a control population [66]. Moreover, an autopsy study of long-term survivors of single moderate-severe TBI found significantly increased p-tau and neuritic Aß plaque pathology compared to uninjured controls suggesting that a single TBI may accelerate the development of AD-type neurodegeneration [67]. In addition to AD, a link has been suggested between TBI and PD. In a case-control study, data from the Rochester Epidemiology Project were used to identify 196 subjects who developed PD and to compare to controls matched for age and gender. The frequency of head trauma was significantly higher in PD cases compared with controls (odds ratio [OR] 4.3). The OR for PD was also substantially increased (11.0) in subjects who experienced mTBI with LOC or more severe TBI [62]. Because Parkinsonian symptoms may result from neuronal loss in the substantia nigra associated with either accumulation of a-synuclein in Lewy bodies, as occurs in PD, or p-tau inclusions in the form of NFTs, as occurs in CTE and AD, it is

possible that multiple pathologies contribute to the increased frequency of Parkinsonism after TBI. Trauma has been considered as a possible trigger of ALS neurodegeneration as well [63,64,68]. Literature points toward a trend not only between CNS trauma and the development of ALS, but also between a smaller number of years between the last injury and ALS diagnosis and older age at the last injury and the development of ALS [64]. In a case-control study of 109 cases of ALS and 255 controls, Chen and colleagues [63] found that having experienced repeated head injuries or having been injured within the 10 years before diagnosis was associated with a more than 3-fold higher risk of ALS (OR 3.1; 95% confidence interval [CI], 1.2–8.1; and OR 3.2; 95% CI, 1.0–10.2, respectively), with a slightly elevated risk for the interval 11–30 years. The authors further performed a meta-analysis of eight previous ALS studies and estimated a pooled OR of 1.7 (95% CI, 1.3–2.2) for at least one previous head injury.

1.2.2. Chronic traumatic encephalopathy—Repetitive mTBI is associated with CTE [8–20]. CTE is clinically characterized by mood and behavioral disturbances, progressive decline of memory and executive functioning, and cognitive deficits that eventually progress to dementia over the course of several decades [14,17,69,70]. Mood and behavioral disturbances typically include depression, apathy, impulsivity, anger, aggression, irritability, and suicidal behavior [14,17,69]. At the present time, there are no validated clinical criteria to aid the clinician in differentiating CTE from AD or any other neurodegeneration associated with aging; however, in CTE, mood and behavioral symptoms often appear in an individual's 20s, 30s, and 40s, ages far younger than the typical age at onset of neurodegenerations such as AD. Similar to many neurodegenerative diseases, CTE can only be diagnosed definitively at postmortem neuropathological examination [14,17,69]. The most commonly observed gross pathologic features of CTE are generalized cerebral atrophy with a predilection for the frontal, temporal, and medial temporal lobes; thalamic and hypothalamic atrophy; shrinkage of the mammillary bodies; enlargement of the lateral and third ventricles; thinning of the corpus callosum; cavum septum pellucidum often with fenestrations; and pallor of the substantia nigra and locus coeruleus [17].

CTE is a tauopathy, and microscopically there are widespread deposits of p-tau protein as NFTs and disordered neurites throughout the brain [14,17]. Two hallmark microscopic features of CTE, features not found in other tauopathies, are that the p-tau pathology in CTE is (1) perivascular and (2) irregularly distributed in clusters at the depths of cortical sulci. P-tau is also commonly found in the subpial astrocytes at the sulcal depths, as astrocytic tangles, and as axonal varicosities and neuropil threads in the white matter.

Studies in athletes suggest that there is a stereotyped progressive increase in p-tau pathology in CTE that increases with time [17]. P-tau pathology begins focally as perivascular clusters of NFTs, usually at the sulcal depths of the frontal, septal, insular, temporal, or parietal cortices (Stage I). As the disease progresses, multiple discrete clusters of perivascular p-tau NFTs are found in the sulcal depths as well as NFTs in the superficial layers of adjacent cortex (Stage II). In Stage II CTE, the nucleus basalis of Meynert and locus coeruleus usually show neurofibrillary degeneration, but the medial temporal lobe structures (entorhinal cortex, amygdala, hippocampus) are generally spared. In Stage III CTE, NFTs are frequent in the medial temporal lobe, and there is spreading involvement of the frontal,

temporal, parietal, insular, and septal cortices. NFTs are usually also found in olfactory bulbs, hypothalamus, thalamus, mammillary bodies, substantia nigra, and raphe nuclei as well as the nucleus basalis and locus coeruleus. In Stage IV CTE, NFTs are distributed widely throughout the brain, with increasing myelinated fiber and axonal loss in the white matter. Axonal loss and myelin pathology is present at all stages of CTE and progresses with CTE severity. Most CTE cases also demonstrate TDP-43 immunoreactive intraneuronal and intraglial inclusions and neurites. Neuroinflammation is another consistent feature of CTE, and activated microglia are found throughout the subcortical white matter accompanied by a robust astrocytosis. b-amyloid (Ab) deposits are only found in 40–50% of CTE cases, are significantly associated with age at death, and are not a characteristic of early CTE. In CTE, Ab is found predominantly as diffuse plaques in low densities. α-Synuclein-positive Lewy bodies are found in approximately 20% of CTE cases and are significantly associated with the age of the subject at death [17].

Of the 110 cases neuropathologically diagnosed with CTE at the Boston VA TBI Brain Bank, CTE has been diagnosed in 23 veterans (Table 1, Fig. 2). Sixteen veterans with CTE were accomplished athletes, including nine former NFL players, one former semiprofessional football player, three former professional boxers, one former Army rugby player, one former Army boxer, and an amateur hockey player. Of those, three were also diagnosed with AD, three with PD, and one with motor neuron disease. Two nonathlete veterans who experienced a moderate to severe TBI from an assault or motor-vehicle accident while in service (one intraparenchymal TBI with persistent, poorly controlled post-traumatic epilepsy, one spinal cord injury) were also diagnosed with CTE (Fig. 2).

1.3. Relationship between postconcussive syndrome, chronic traumatic encephalopathy, and posttraumatic stress disorder

It has been increasingly recognized that there is a frequent association of mTBI and PTSD in modern warfare [2]. Of 2525 U.S. Army infantry soldiers surveyed after deployment to Iraq for 1 year, 44% of the soldiers with mTBI and subsequent LOC met criteria for PTSD [2]. However, it is often difficult to distinguish PTSD from PCS [72], and there is considerable overlap between PTSD and CTE, especially in the early stages. Combining our experience at VA Boston with that of Omalu [19], 80% (4 of 5) of OIF/OEF/OND veterans exposed to blast injury with neuropathologically verified early CTE were also diagnosed with PTSD. PCS, CTE, and PTSD are all characterized by neuropsychiatric symptoms indicative of frontal lobe dysfunction, including alterations in working memory, planning, multitasking, complex decision-making, judgment, empathy, executive function, impulsivity, emotional lability, and disinhibition, as well as changes in personality, social behavior, and sleep [72,73]. Recently, using a model of blast overpressure injury in rats, Elder and colleagues demonstrated that blast injury induced under anesthesia produced PTSD-related behavioral traits, suggesting that the biological aspects of blast injury could evoke PTSD behaviors in the absence of psychological stressors [74].

The co-occurrence of symptoms of mTBI, PCS, PTSD, and CTE; the symptom overlap among the disorders; and accumulating evidence that the neuropathological foundations of each may be more convergent than previously recognized have fu eled controversies

regarding how to best to provide care for veterans and military service members. Clearly, understanding the importance of microstructural physical brain injury to persistent symptoms after mTBI and the role of physical injury in producing or augmenting psychological stress is a focus of investigation that will help guide proper diagnosis, therapy, and management for veterans.

2. Conclusion

Understanding the effects of military-related mTBI presents numerous challenges. Military mTBI is diverse and diffi-cult to assess, and no validated, objective biomarkers of the acute injury exist. Acute mTBI, whether from concussion or blast, is characterized by physical changes in the brain, including multifocal axonal injury, microvascular damage, neuroinflammation, and elevations in p-tau. Although these changes are generally considered to be reversible and to improve or resolve with time and rest, no well-established methods to monitor status or judge prognosis have yet been identified. Understanding rehabilitative strategies or treatments that will facilitate more rapid and complete recovery from acute mTBI are obviously needed; these restorative practices might well focus on mechanisms that promote innate neuroplasticity, such as graded exercise, restorative sleep, and nutritional support. Repetitive mTBI can sometimes provoke the development of CTE, as has been demonstrated in veterans of the Iraq and Afghanistan conflict exposed to explosive blast and in other veterans who were exposed to repetitive concussive injury often in conjunction with the play of sports. The contributionof genetic, environmental, and other exposure factors to the risk of CTE after mTBI remains to be determined. In addition, some individuals with CTE are also diagnosed with PTSD, illustrating the symptom commonalities between the two disorders and possibly signifying shared pathogenetic foundations. The development of a new national PTSD brain bank, under the auspices of the National Center for PTSD, in conjunction with continued neuropathological analysis of mTBI, will promote better understanding of the neuropatho-logical, biochemical, and molecular underpinnings of PTSD, mTBI, and CTE and the interrelationship among the disorders.

Acknowledgments

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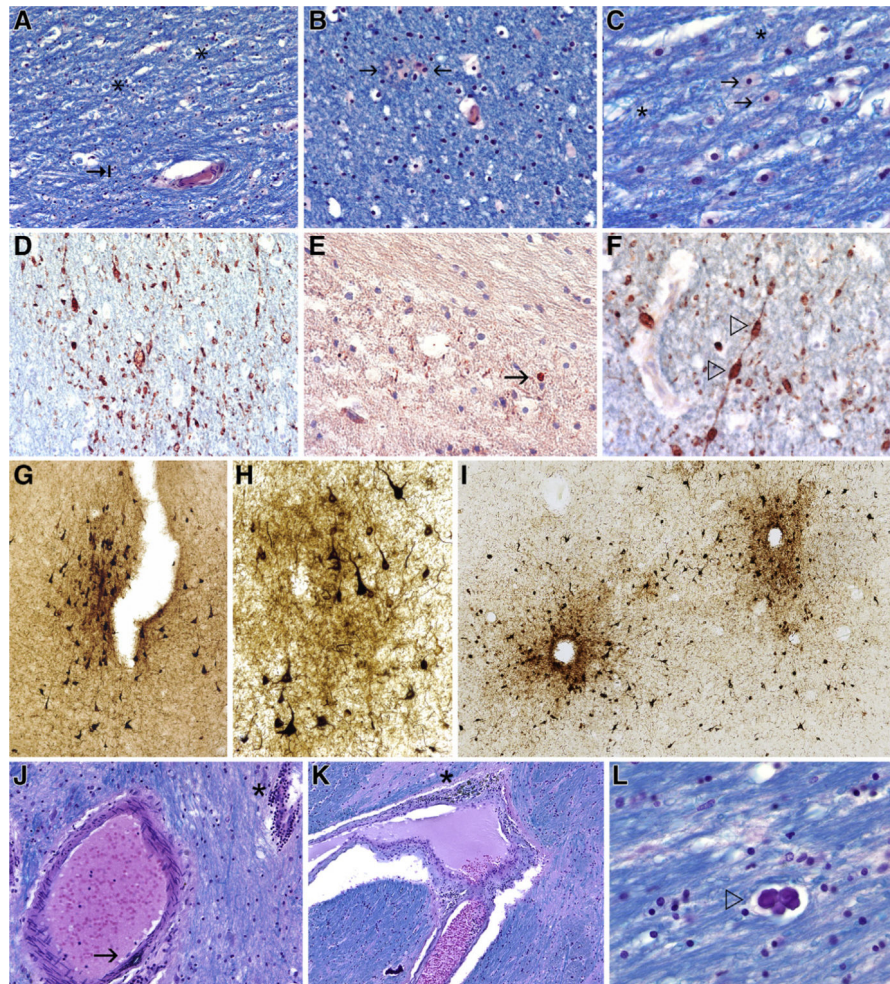
Fig. 1.
Neuropathological changes associated with blast injury. (A–C). Subcortical frontal white matter shows loss of myelinated fibers, abnormal myelin clumps (asterisks), and astrocytosis (arrows), case 1, luxol fast blue-hematoxylin and eosin stain, original magnification (A) ×200, (B) ×400, and (C) ×600. (D) Axons in the frontal white matter are severely depleted with many irregular axonal swellings, case 1, SMI-34 immunostaining, original magnification ×400. (E) APP immunostaining shows axon retraction bulbs and other axonal irregularities (arrow), APP immunostaining, case 1, original magnification ×400. (F) Axonal swellings, case 1, SMI-34 immunostaining, original magnification ×600. (G) A single focus of perivascular NFTs and neurites at the depth of sulcus in inferior parietal cortex consistent with Stage I/IV CTE, case 1, AT8 immunostaining for hyperphosphorylated tau (p-tau), original magnification ×100. (H) Perivascular NFTs at the sulcal depths of frontal cortex, case 3, AT8 immunostaining, original magnification ×200. (I) Multiple areas of perivascular NFTs, case 2, AT8 immunostaining, original magnification ×100. (J) Small blood vessels in the thalamus show prominent perivascular lymphocytic cuffing (asterisk) whereas a neighboring medium-sized artery shows focal degenerative calcification of the blood vessel wall (arrow), case 4, luxol fast blue-hematoxylin and eosin stain, original magnification ×200. (K) A medium-sized vessel in the thalamus shows lymphocytic infiltration of the

vascular wall with hemosiderin-laden macrophages (asterisk), case 4, luxol fast blue-hematoxylin and eosin stain, original magnification ×200. (L) Focus of dystrophic calcification in the white matter (open triangles), case 4, luxol fast blue-hematoxylin and eosin stain, original magnification ×400. APP, amyloid precursor protein; NFTs, neurofibrillary tangles; CTE, chronic traumatic encephalopathy.
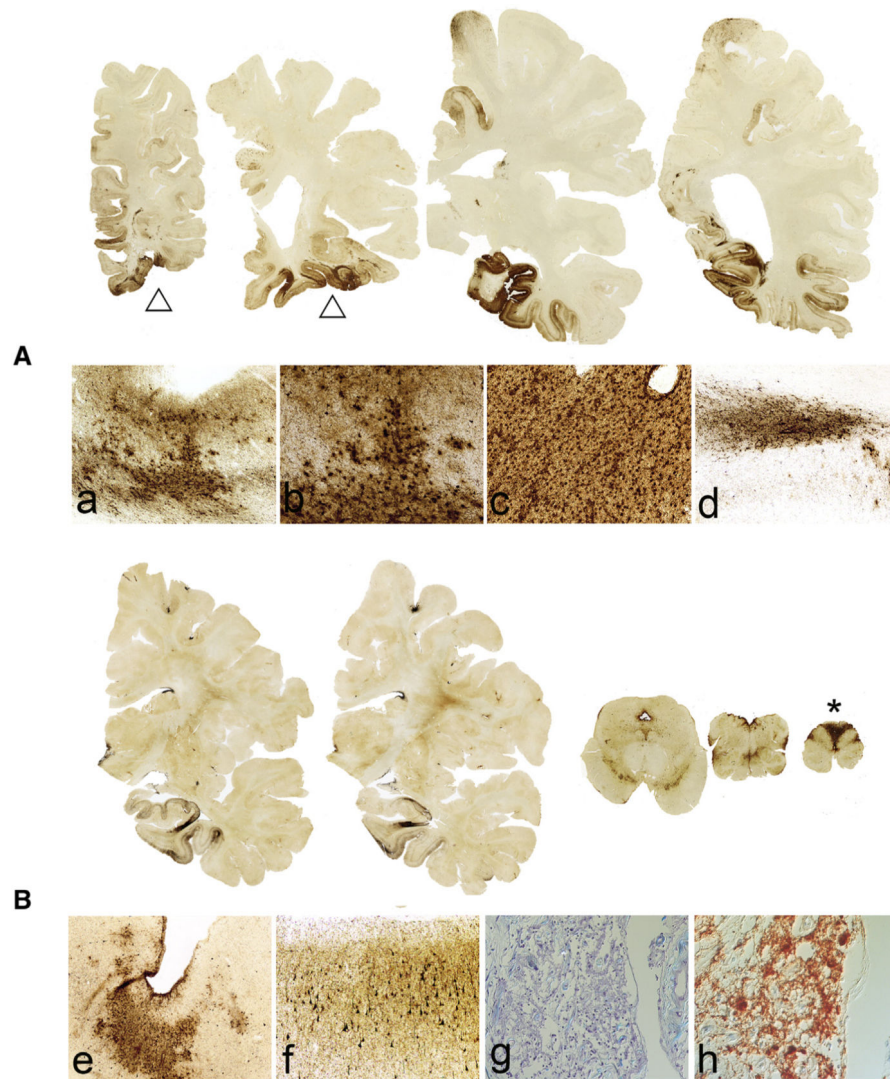
Fig. 2.
CTE in two nonathlete veterans. (A) A 77-year-old veteran experienced a severe TBI with LOC during an assault while in service, resulting in intraparenchymal cystic cavities with calcification in the left inferior frontal cortex, left hippocampus, and left calcarine cortex (open triangles). Afterward, he developed poorly controlled posttraumatic grand mal epilepsy that resulted in multiple visits to the emergency department for mTBI. At autopsy, he was found to have a marked tauopathy, most severe in the areas surrounding the traumatic lesions, which was strikingly perivascular, most severe at the depths of the sulci, and affected the white matter and subpial regions. (A) Whole-mount, AT8-immunostained, free-floating coronal sections, original magnifications (a) ×100, (b) ×200, (c) × 200, and (d) ×100. (B) An 82-year-old veteran suffered a TBI and cervical spinal injury in a motor-vehicle accident while in service. Upon discharge, he was involved in multiple assaults as a police officer that eventually resulted in permanent disability and quadriplegia. At autopsy, his brain showed p-tau-immunoreactive NFTs and neurites in an irregular, multifocal distribution in the frontal and temporal cortices, with a predilection for sulcal depths and

perivascular, periventricular, and subpial regions diagnostic of Stage III/IV CTE. The posterior columns in the medulla showed intense p-tau immunoreactivity (asterisk). In addition, his cervical spinal cord from C2 and below was replaced by loose neuroglial tissue that showed intense immunoreactivity for p-tau. (B) Whole mount, AT8-immunostained, free-floating coronal sections: (e) irregular clusters of p-tau NFTs at depths of sulcus, original magnification !40; (f) p-tau NFTs in the superficial frontal cortex, original magnification ×100; (g) loose neuroglial tissue at C2 level of the spinal cord, luxol fast blue-hematoxylin and eosin stain, original magnification ×200; (h) neuroglial tissue at C2 level of the spinal cord, AT8 immunostaining, original magnification ×200. CTE, chronic traumatic encephalopathy; TBI, traumatic brain injury; LOC, loss of consciousness; p-tau, hyperphosphorylated tau.

Table 1

Subject demographic information

Subject	Age, years	Race/ethnicity	Sex	Exposure to TBI	CTE stage	Other pathology	Cause of death	PTSD
1	60-69	C	Male	NFL	IV	AD	FTT	
2	70-79	C	Male	NFL	IV	AD	FTT	
3	80-89	C	Male	Amateur hockey	IV	AD, PD	FTT	
4	70-79	C	Male	NFL	IV	PD	Cardiac	
5	70-79	C	Male	NFL	IV		FTT	
6	80-89	AA	Male	NFL	IV		FTT	
7	80-89	AA	Male	NFL	IV		Respiratory failure	
8	70-79	C	Male	NFL	IV		Respiratory failure	
9	80-89	C	Male	NFL	II		Cardiac	
10	90-99	C	Male	NFL	IV		FTT	
11	80-89	C	Male	Semiprofessional football	IV		FTT	
12	60-69	C	Male	Army rugby	IV	PD	FTT	
13	70-79	C	Male	Professional boxing	IV		FTT	
14	70-79	AA	Male	Professional boxing	IV		Pneumonia	
15	90-99	C	Male	Professional boxing	IV		FTT	
16	40-49	C	Male	Army boxing	III	MND	Respiratory failure	
17	80-89	C	Male	Assault, posttraumatic epilepsy	III		Pneumonia	
18	70-79	C	Male	MVA, assaults	III		Pneumonia	
19	20-29	C	Male	IED blast	I		GSW	PTSD
20	20-29	H	Male	IED blast, HS football	I		Hemorrhage	PTSD
21	40-49	C	Male	IED blast	II		Aneurysm	
22	30-39	C	Male	IED blast, HS football	II		Overdose	PTSD
23	20-29	C	Male	Military concussion, HS football	I		Suicide	PTSD

Abbreviations: AA, African American; AD, Alzheimer's disease; C, Caucasian; CTE, chronic traumatic encephalopathy; FTT, failure to thrive; GSW, gunshot wound; H, Hispanic; HS, high school; IED, improvised explosive device; NFL, National Football League professional football; PD, Parkinson's disease; PTSD, posttraumatic stress disorder; MND, motor neuron disease.