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Original Articles

Long-Term Consequences of Traumatic Brain Injury: Current Status of Potential Mechanisms of Injury and Neurological Outcomes

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Abstract

Traumatic brain injury (TBI) is a significant clinical problem with few therapeutic interventions successfully translated to the clinic. Increased importance on the progressive, long-term consequences of TBI have been emphasized, both in the experimental and clinical literature. Thus, there is a need for a better understanding of the chronic consequences of TBI, with the ultimate goal of developing novel therapeutic interventions to treat the devastating consequences of brain injury. In models of mild, moderate, and severe TBI, histopathological and behavioral studies have emphasized the progressive nature of the initial traumatic insult and the involvement of multiple pathophysiological mechanisms, including sustained injury cascades leading to prolonged motor and cognitive deficits. Recently, the increased incidence in age-dependent neurodegenerative diseases in this patient population has also been emphasized. Pathomechanisms felt to be active in the acute and long-term consequences of TBI include excitotoxicity, apoptosis, inflammatory events, seizures, demyelination, white matter pathology, as well as decreased neurogenesis. The current article will review many of these pathophysiological mechanisms that may be important targets for limiting the chronic consequences of TBI.

Key words: atrophy; inflammation; neurogenesis; progressive damage; TBI; white matter

Introduction

Traumatic brain injury (TBI) produces both acute and more chronic consequences that lead to permanent disabilities that increase long-term mortality and reduced life expectation.[1–4] The direct consequences of a single TBI or repetitive insults can result in various secondary pathological conditions, including seizures, sleep disorders, neurodegenerative diseases, neuroendocrine dysregulation, and psychiatric problems.[5–13] Changes initiated by TBI can persist for months or years after injury and significantly affect quality-of-life issues in these patients. Our current understanding of the pathophysiology of TBI has emphasized the multi-factorial nature of injury events that are activated by TBI. Indeed, many preclinical, as well as some clinical, studies have evaluated various therapeutic interventions to target both the acute and more chronic consequences of TBI with some degree of success.[14–22] In this regard, neuroprotective, as well as treatment, strategies that target abnormally sustained elevations in intracranial pressure have been attempted. However, currently, there are limited therapeutic interventions that have been shown to improve the long-term consequences of TBI.[20,23] This is a growing problem because of the increased incidence of TBI in many countries, including a growing incidence of concussion in sport- and military-related activities.[24–26]

The fact that acute injury can lead to long-term consequences, including progressive brain atrophy and an increased vulnerability to neurodegenerative disorders, is a critical problem. In some models of TBI, immunocytochemical evidence for chronic traumatic encephalopathy (CTE) has been presented.[11,25,27] Indeed, several studies have emphasized that months to years after injury, evidence for progressive gray and white matter (GM/WM) atrophy is observed after TBI (Fig. 1).[14,28–34] Similar observations have been shown in TBI patients using computed tomography and magnetic resonance imaging (MRI) modalities (Fig. 2).[2,35–41] Underlying mechanisms for these progressive injuries emphasize the complex nature of this disease process and require a multidisciplinary approach to clarifying and targeting multiple injury cascades associated with different injury severities.[1] Original articles and review articles have summarized the histopathological and behavioral consequences of TBI that have been described in various animal models. Recently, the importance of repetitive episodes of mild TBI have also been emphasized in the trauma literature. Various publications have demonstrated the potential for repetitive insults producing cumulative effects and leading to long-term consequences, including age-related neurodegerative disorders (i.e., CTE and Alzheimer's disease [AD]). The aim of this article is to review the pathomechanisms that have been attributed to the

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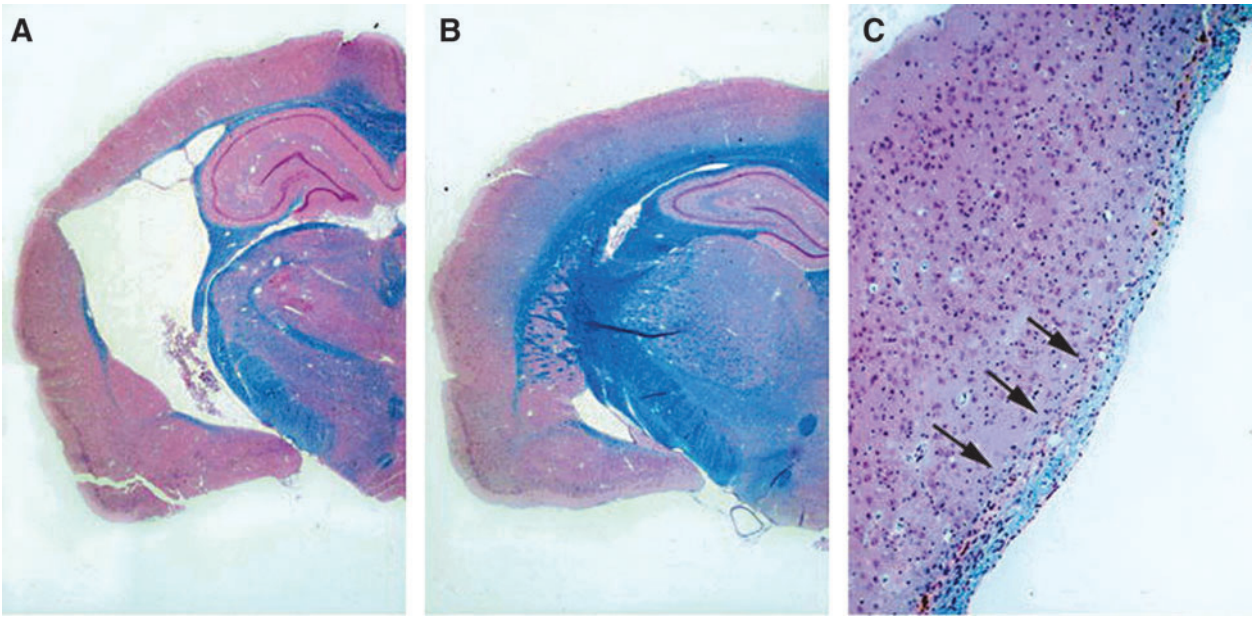

FIG. 1. Double-stained hematoxylin-eosin and Luxol-fast blue sections 1 year after traumatic brain injury (TBI) or sham procedure. (**A**) TBI animal showing gross atrophy with marked expansion of the ipsilateral lateral ventricle. (**B**) Sham-operated animal appearing unremarkable. (**C**) Higher magnification of external capsule thinning (arrows) after TBI. Reprinted from Bramlett and Dietrich (2002), with kind permission of Springer Science and Business Media.

progressive nature of TBI. The wide range of pathophysiological processes that have been implicated clearly emphasize the complexity of TBI in terms of patterns of cell vulnerability, sustained secondary injury processes, as well as endogenous reparative processes after injury (Fig. 3).[42] Below, injury processes are discussed in terms of current research knowledge and potential therapeutic interventions targeting these processes.

Excitotoxicity

One of the initial pathomechanisms that was investigated to target neuronal vulnerability after cerebral ischemia or trauma was neuronal excitotoxicity.[43] Early studies showed that neurons as well as oligodendrocytes were highly vulnerable to glutamate receptor activation and that selective inhibitors of specific glutamatergic receptors could provide protection in terms of cell death.[44–46] Subsequent to TBI, many studies have emphasized that excitotoxic processes participate in the pathophysiology and have reported neuroprotection with treatments that block these specific receptors.[47–54] Regional microdialysis studies have reported on early elevations in the extracellular levels of excitatory amino acids, including glutamate, that appear to be dependent on both injury severity as well as a number of physiological variables.[53,55–57] In the 1990s, numerous studies reported that treatments directed toward N-methyl-D-aspartate receptor (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation were protective in models of TBI.[58–60]

Studies have also assessed whether receptor plasticity in vulnerable brain regions may increase the vulnerability of cells at chronic periods after brain injury.[61] Indeed, recent evidence indicates that oligodendrocyte vulnerability may be delayed after brain or spinal cord injury (SCI) and could involve excitotoxic cell death mechanisms leading to vulnerability of myelin-producing cells and progressive demyelination.[39,62] Demyelination has been documented in models of TBI as well as a variety of other types of central nervous system (CNS) disorders including multiple sclerosis, stroke, and schizophrenia.[28,63] More recently, a new approach to targeting NMDA receptors has been advanced, where stimulation of the receptor in the subacute period after TBI has been reported to be beneficial.[64] Strategies that target these acute and more chronic excitotoxic processes continue to represent potential strategies for reducing the long-term consequences of circuit dysfunction after TBI.

Reactive Oxygen Generation

Experimental and clinical studies have emphasized the importance of generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as occurring in the early post-traumatic stages of the injury process.[65–67] Oxidative stress (OS) leads to irreversible neuronal membrane damage, resulting in a pattern of secondary injury mechanisms ultimately leading to dysfunction and cell death. A variety of OS markers have been evaluated in models of TBI, including carbonylated proteins, lipoperoxides, ROS, and RNS, whereas antioxidant defense enzymes decrease after trauma.[68,69] Thus, the imbalance produced by the injury environment between oxidant and antioxidant agents is an important target in the development of new therapeutic interventions that could improve outcome and antioxidant strategies have been developed and tested.[70–73] Selective poly (ADP-ribose) polymerase 1 inhibition decreases the generation of ROS and proinflammatory cytokines.[74] In terms of injury severity, generation of ROS indicates that severity plays a major role in oxidant and antioxidant balance.[75] Ongoing studies using sensitive indicators of OS continue to be developed and analyzed to determine the importance of these ongoing injury cascades in progressive damage after TBI.[76,77]

In terms of molecular mechanisms underlying OS, recent investigations have concentrated on the transcription factor, nuclear factor erythoid-related factor 2 (NRF2), that mediates antioxidant and cytoprotective genes by binding two antioxidant response

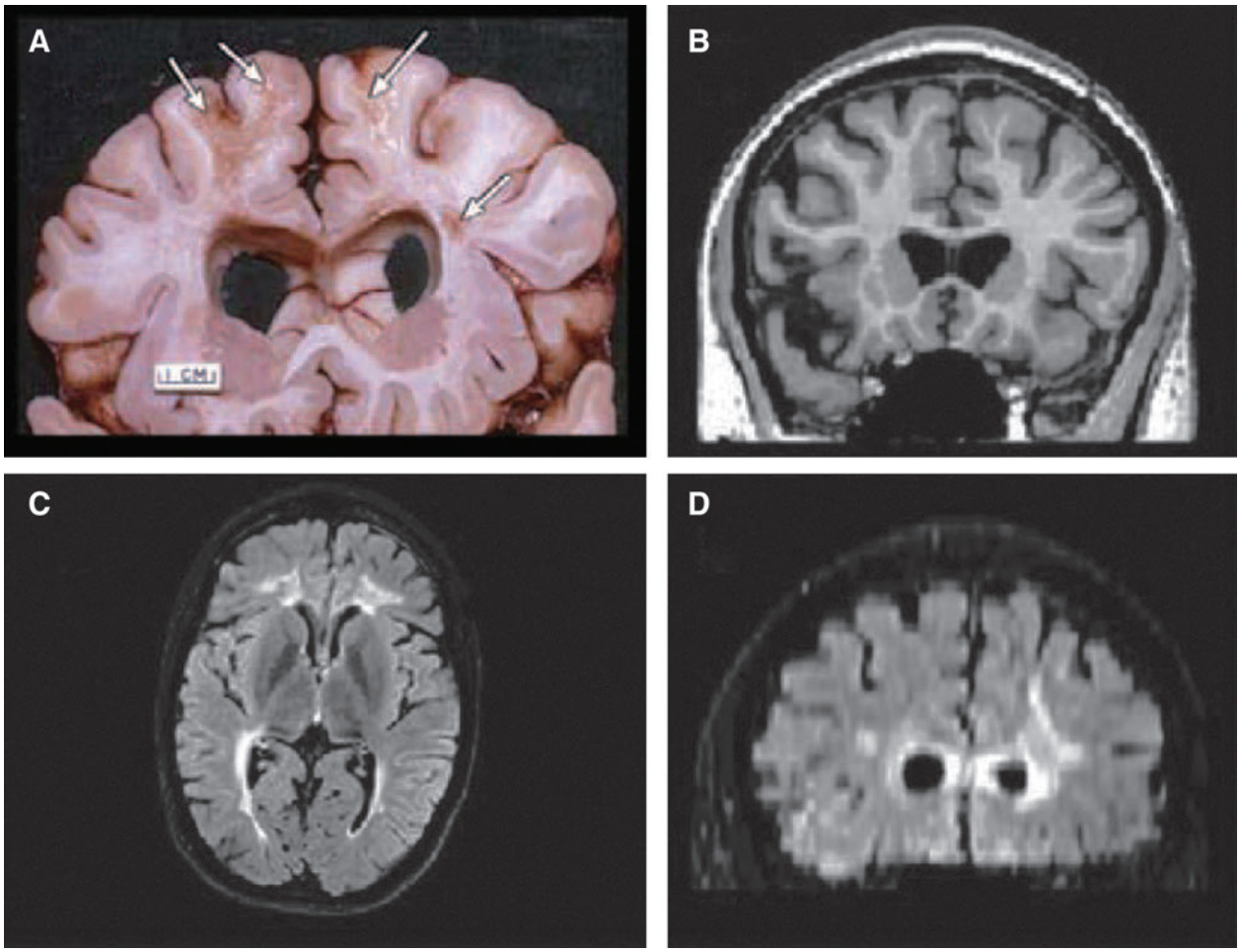

FIG. 2. (**A**) Postmortem from a patient who survived 7 years after severe TBI. Note the dilated ventricles, focal areas of white matter (WM) degeneration (arrows), atrophic corpus callosum, and prominence of the interhemispheric and Sylvian fissures reflective of generalized cortical atrophy. (**B**) Similar-level T1 MRI coronal section depicting comparable ventricular dilation, and also note the prominence of the cortical sulci and Sylvian fissure as well. (**C**) Axial fluid-attenuated inversion recovery (FLAIR) sequence depicting bilateral WM signal abnormality. (**D**) Resliced from the axial acquisition of the FLAIR sequence, this coronal FLAIR image shows extensive WM changes in the periventricular and deep WM of the frontal lobes, in association with the dilated ventricles. The focal areas of WM degeneration that can be seen in (A) will display as signal abnormality in the WM as shown in (D). Reprinted from Bigler and Maxwell (2011), with kind permission of IOS Press.

elements (AREs).[77] In one study, NRF2 messenger RNA was reported to increase after focal TBI. In another study, administration of the NRF2-ARE activators, sulforaphane and carnosic acid, protected mitochondria *in vivo* from toxic exposure in the subacute phase after TBI.[76] Using a model of cortical impact injury, treatment with phenelzine scavenger lipid pro-oxidation prevented respiratory depression effects in cortical mitochondria. Hughes and colleagues[72] recently reported protection in a TBI model by genepin, a fruit extract. The continued development of novel antioxidant therapeutic strategies is an active area of neurotrauma research, with new studies suggesting that combination treatments including complimentary antioxidants may be required to protect against the long-term consequences of TBI.[65]

Apoptosis

Apoptosis is a mechanism underlying programmed cell death that has been characterized in models of brain injury and SCI. Molecular indicators of apoptosis, including activation of intrinsic and extrinsic apoptotic pathways, have been reported in several models of TBI.[78,79] More recently, biomarker studies have reported that proapoptotic proteins are up-regulated in plasma and cerebrospinal fluid (CSF) samples from TBI patients.[80,81] In contrast to necrosis, apoptotic cell death is commonly felt to be delayed and more prolonged.[82] Thus, apoptotic cell death of neuronal or myelin-producing cells is a potential mechanism for the progressive nature of TBI. Indeed, evidence of delayed apoptosis of oligodendrocytes has been reported using immunocytochemical (ICC) analysis of brain tissues weeks to months after injury.[83,84] These data indicate that delayed apoptotic cell death, as well as other programmed cell death mechanisms, currently being investigated in the laboratory could underlie some of these long-term consequences of brain injury.

Various strategies have been utilized to target apoptotic cell death after brain injury. Nonspecific apoptotic inhibitors have been reported, in some studies, to be protective after TBI and to be associated with improved behavioral outcome.[21,85–87] In contrast, other studies have reported only transient protection with these

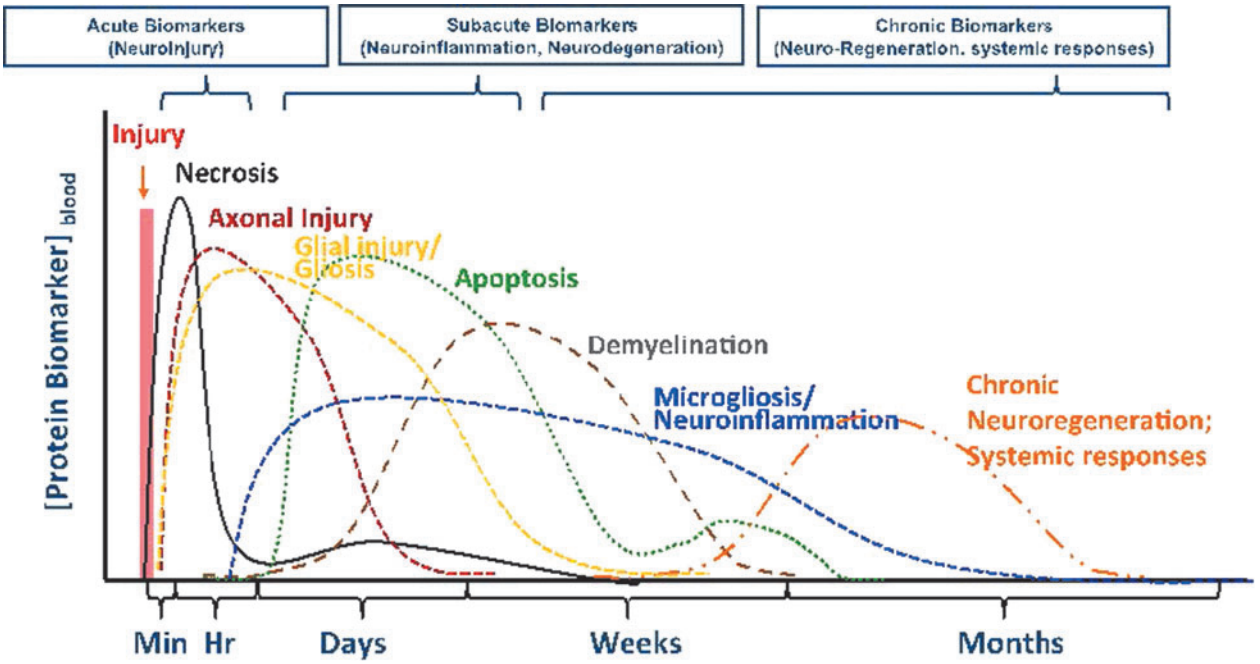

FIG. 3. Continuum of biomarkers for TBI pathophysiology and its manifestation over time. Reprinted from Wang and colleagues (2013), with kind permission of the Society of Photo-Optical Instrumentation Engineers (SPIE).

inhibitors, and, currently, more-selective antiapoptotic molecules are being developed and tested.[88–90] Because of the importance of apoptotic cell death in injury models, this is an important therapeutic target for limiting the long-term consequences of TBI.

Inflammation

Inflammatory processes have long been viewed as important secondary injury mechanisms after TBI.[91] Numerous studies have reported, in models of TBI, evidence for acute and more chronic inflammatory events that, in specific cases, are felt to lead to secondary damage and long-term neuronal disorders.[27,92–95] Evidence for activation of intrinsic inflammatory cells, including microglia, as well as recruitment of circulating inflammatory cells and macrophages into injured tissue, have been described in both experimental and clinical tissues.[34,92,96–98] These inflammatory cells are associated with increased synthesis of a variety of chemokines and cytokines that can be proinflammatory and thus potentially neurotoxic. Biochemical analyses have indicated that increased elevations in tissue levels of interleukin (IL)-1β, tumor necrosis factor alpha (TNF-α), IL-6, and transforming growth factor as well as many others are observed at various times after TBI.[93,99] Recent evidence has also been provided for increased inflammasome activation after TBI, an important innate immune regulator of inflammatory events active after several neurological conditions.[100,101]

In clinical studies, biomarker analysis has also provided direct evidence for inflammatory processes being active in various TBI patients weeks to months after injury.[102,103] Elevated levels of IL-1 have been reported weeks after TBI, indicating that active inflammatory events are still apparent in the later TBI stages.[104] Histopathological evaluation of human tissues after TBI has also provided direct evidence for prolonged inflammatory events.[96,105] For example, evidence for activated microglia in WM tracts years after brain trauma has been emphasized in human brain specimens.[106,107] Although inflammatory processes can have both damaging, as well as reparative, consequences, abnormal inflammation remains an important target for reducing the long-term consequences of TBI.

Experimental and clinical studies evaluating receptor blockers against IL-1β are showing some encouraging results.[108–114] Other published studies using progesterone or anti-inflammatory steroids appear to show some promise in the clinical literature.[115] In the area of therapeutic hypothermia, a number of published studies have reported that the beneficial effects of early cooling and temperature management strategies appear to be relevant to targeting inflammatory events after TBI.[116] Several studies, for example, have shown that therapeutic hypothermia in models of TBI reduce levels of the TNF-α and IL-1β families of inflammatory genes as well as abnormal inflammasome activation.[117–122] Future studies are required to determine factors associated with prolonged inflammatory events as well as appropriate therapeutic targets for reducing the detrimental consequences of inflammation.

A relatively new development in the area of inflammatory cascades after TBI is the discovery that inflammatory cells are relatively plastic and may participate in both neurodegenerative, as well as reparative, processes.[123–125] Distinct microglia/macrophage subsets can be classified in four main phenotypes: classically activated M1 phenotype with cytotoxic properties; alternative activated M2A phenotype, with proregenerative functions; M2B immunoregulatory phenotype; and the M2C deactivated phenotype surface antigens that recognize specific functions.[126,127] The importance of microglia/macrophage polarization patterns has been reported in several experimental conditions with the heterogeneity of the inflammatory cell responses to trauma emphasized.[123,128] Currently, novel approaches to reduce excitotoxic and growth-limiting inflammatory phenotypes while promoting those that promote reparative processes are currently being evaluated. In this regard, pharmacological strategies that limit proinflammatory M1 phenotype while promoting the anti-inflammatory M2 phenotype and thereby modifying the M1/M2 macrophage ratio have

implications for brain protection and repair. Recently, specific molecules, including pattern receptor recognition receptors, integrins, cytokine/chemokines, nuclear receptors, and galectins, have been shown to be important signaling pathways affecting both immune and neuronal cells.[123] Markers of neuroinflammation can persist in the brain parenchyma up to 16 years after TBI, and recent evidence for chronic immune activation associated with behavioral deficits, including chronic depression, has been documented.[96,129]

Post-Traumatic Epilepsy and Cortical Spreading Depolarizations

Post-traumatic epilepsy (PTE) is a major consequence of TBI occurring in approximately 25% of patients with severe TBI.[5] Clinical studies have documented the incidence of PTE showing that these periods of abnormal neuronal excitation can occur weeks, months, or years after injury.[130–132] Importantly, PTE is an important secondary injury mechanism that can aggravate damage or impede endogenous recovery mechanisms.[133–139] In one experimental study, induced periods of PTE were shown to increase the vulnerability of cortical and subcortical structures after experimental TBI.[135] This study first emphasized the potential for a brief episode of PTE to have a significant impact on the vulnerability of the post-traumatic brain. Because recent clinical data have emphasized the high incidence of PTE and episodes of cortical spreading depolarization in TBI patients, these post-traumatic events require more investigation.[140] Currently, various strategies are being evaluated, including single or combinatorial drug therapies, as well as therapeutic hypothermia to target these episodes of circuit excitation.[15,141,142]

More recent data have emphasized the incidence of subclinical (nonconvulsive) seizures after TBI that, although not routinely documented in the human population, can be recorded using monitoring procedures, including long-term electroencephalography surface recordings.[131,143] Investigators have described a high incidence of subclinical seizures that appear in patients at variable periods after TBI.[131] This is an important finding given that subclinical seizures in the TBI population could represent an important secondary injury mechanism leading to long-term consequences, including circuit dysfunction and neuronal cell death.[144] In studies being conducted in pre-clinical models, evidence for subclinical seizures has also been documented.[143,145] Using noninvasive long-term monitoring in awake rats after TBI, for example, evidence for patterns of abnormal EEG activity is observed at various post-traumatic periods.

In addition to PTE, episodes of cortical spreading depolarization (CSD), as mentioned previously, are also observed in models of brain injury.[146–149] There is a rich history of evidence showing that repetitive episodes of CSD can represent a secondary injury mechanism in models of focal cerebral ischemia and trauma that may increase the vulnerability of neuronal populations surrounding areas of contusive brain injury.[148] Most recently, evidence for repetitive episodes of CSD has been reported in patients after stroke and TBI.[146,150] Thus, repetitive episodes of CSDs are another potential mechanism of secondary injury that can continue to affect the manner in which the brain responds to trauma long after the traumatic insult. Episodes of CSD have been shown to be sensitive to selective pharmacological treatments, including NMDA receptor and calcium antagonists.[151–153] Also, previous data have indicated that CSD episodes are sensitive to brain temperature.[154,155] Additional experimental and clinical data are therefore required to determine the incidence of CSD in various TBI patient populations and the testing of novel treatment strategies targeting episodes of PTE and CSD in patients who could benefit in terms of long-term outcomes.

Subsequent to TBI, bleeding within the neuropil leads to hemolysis and the deposition of hemoglobin.[156,157] A recently proposed mechanism for development of PTE is that iron compounds deposited in brains of TBI patients form reactive free radical oxidants, leading to release of glutamate and subsequent abnormal neuronal excitation.[157,158] Comprehensive gene expression and gene network analyses have also clarified molecular events associated with PTE and reported up-regulation of phosphatase A2 and lipid metabolism, which may be related to seizure propagation.[139,158] Importantly, administration of antioxidants appears to cause an interruption of the generation of chronic seizures induced by hemorrhage.[157]

Calpain-Mediated Proteolysis

TBI produces a prolonged activation of calpains resulting in the proteolysis of numerous cellular substrates, including cytoskeletal components and membrane receptors.[159–163] Using both *in vitro* and *in vivo* models, calpain-specific breakdown products, including α-spectrin, are observed within axonal, dendritic, and somatic regions after injury, leading to transport disruption and secondary axotomy.[164] Recently, specific spectrin breakdown products have been reported to be present in CSF from traumatized animals and humans, representing a useful biomarker to assess injury severity and pathophysiological events.[160,165] Indeed, direct relationships between calpain-mediated proteolysis and injury severity have been associated with neurodegenerative and restorative responses.[162]

Multiple strategies targeting calpain breakdown have been used to target the acute and more chronic consequences of CNS injury. Intravenous administration of calpain inhibitors, such as MDL-28170, protect against axonal pathology, as well as neuronal damage, in some experimental models.[166,167] More recently, transgenic mice overexpressing calpastatin demonstrate reduced calpain-mediated spectrin proteolysis after TBI with some benefits in functional outcome.[159,168] Based on current literature, future research should include the continued development and testing of specific, long-lasting inhibitors of calpain-mediated proteolysis.

Diffuse axonal injury

WM injury is a hallmark of TBI, with pre-clinical and human autopsy data demonstrating axonal injury in conditions of both focal as well as diffuse brain injury.[169] Experimental and clinical studies have used a variety of ICC markers, including β-amyloid precursor protein, to demonstrate evidence of early and progressive axonal injury, subsequent deafferentation of cellular targets, Wallerian degeneration, as well as circuit remodeling.[14,27,28,30–33,35,37–40,170–173] Also, using special silver stain, several studies have emphasized the widespread degree of damage to neuronal processes, connections, and the microenvironment produced by TBI.[174,175] One question that is sometimes difficult to answer is whether these progressive axonal changes are the result of primarily Wallerian degeneration or more-active secondary injury mechanisms.[31,33,176–179] In human specimens, evidence for diffuse axonal injury throughout the corpus callosum fibers was first shown to be a common indicator of TBI.[37] The degree of axonal injury appears to be injury-severity dependent and a potentially important cellular event that underlies many of the functional consequences of TBI. Progressive WM damage is also a hallmark of TBI, with MRI approaches showing reduced WM

volumes over time as well as other indicators of axonal damage. State-of-the-art imaging approaches clarifying WM damage using diffusion tension imaging and anisotropy are also providing evidence for subtle changes in the microenvironment and axonal structure, which could underlie some of the long-term progressive changes and prolonged functional disturbances reported in current animal models and in humans.[39,40,172]

In addition to axonal damage, evidence for abnormal axonal sprouting of specific neural populations is also reported in models of TBI.[180–183] Subsequent to axonal damage, multiple imaging approaches have shown evidence for fiber sprouting that could represent reparative events associated with recovery mechanisms.[184–186] In recent studies using genetic mouse models to identify vulnerable cortical neurons after TBI, researchers have described evidence for progressive axonal sprouting extending into deeper cortical regions.[184] The long-term functional consequences of these potentially reparative processes are unknown. It is important to note that in the area of post-traumatic epilepsy, evidence for axonal sprouting has also been demonstrated in the hippocampal mossy fiber pathway.[15,136,183,187] In animal and human studies, where repetitive episodes of seizure activity occur, mossy fiber sprouting has been reported as evidence for abnormal axonal growth to specific targets.[15,181,183] In this particular case, aberrant hippocampal sprouting may participate in some of the mechanisms associated with abnormal excitation and seizure activity.

Several investigations have evaluated therapeutic interventions that may target axonal pathology. These include strategies targeting excitotoxicity, free radical generation, or combination approaches that may be directed at multiple pathomechanisms. Recent evidence has also indicated that therapeutic hypothermia may prevent axonal pathology in several models of TBI.[188–191] A greater understanding of the pathophysiology of axonal damage, both in the acute and more progressive state, is required to clarify how best to treat WM vulnerability after brain injury.

Demyelination and White Matter Loss

As previously described, a variety of WM changes are observed after TBI in both experimental and clinical investigations. Subsequent to TBI, evidence for local demyelination associated with these WM changes has also been emphasized.[29,32,39,84,192] In animals where survival has been allowed up to 1 year after TBI, significant evidence of WM atrophy and demyelination has been reported.[28,30,31,33] Demyelination can occur as a result of several mechanisms, including primary axonal damage and subsequent Wallerian degeneration or death of myelinating cells. Indeed, in a recent publication, oligodendrocyte cell death by apoptotic-dependent mechanisms was demonstrated after a moderate TBI injury.[84] These and other studies emphasize that, in addition to primary axonal damage, axonal demyelination may also underlie some of the more progressive consequences of TBI. Importantly, because myelination is critical to the normal role of axons in terms of the complex function of neuronal circuits, demyelination could underlie many of the long-term functional consequences of brain injury.[193] Strategies to protect against oligodendrocyte cell death, as well as progressive demyelination, include therapeutic interventions targeting excitotoxicity, apoptosis, as well as inflammation. Emphasis needs to be placed on demonstrating evidence for demyelination in our TBI population using state-of-the-art imaging approaches determining the importance of this cellular response in terms of acute and more long-term TBI outcomes.

Adult Neurogenesis

Previous studies have emphasized the occurrence of ongoing neurogenesis in specific areas of the adult brain.[194,195] These regions include the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus. Current research efforts are directed to evaluating the importance of adult neurogenesis on normal cognitive function and integration of new memories into our neural circuits.[196–198] In a recent investigation, direct evidence for adult neurogenesis occurring in humans was obtained from human specimens, where above-ground nuclear bomb testing allowed for determination of neuronal cell birth.[199] Importantly, this study emphasized that sustained neurogenesis occurs in the hippocampus, thus supporting a role for adult neurogenesis participating in hippocampal-dependent learning and memory both during normal aging and after brain injury.

In this regard, several laboratories have reported that after TBI, there is a significant increase in cell proliferation and neurogenesis in the hippocampus using a variety of ICC approaches.[200–203] Several studies have reported increased bromodeoxyuridine (BrdU) cell staining in the SVZ and SGZ after TBI.[15,204,205] Single- and double-label ICC procedures using BrdU and doublecortin staining, along with quantitative NeuN counts, have reported that a population of these proliferating cells turn into immature neurons and, over several weeks, differentiate into mature neurons that integrate into the granular cell circuitry.[201,203,206] In terms of the significance of this cellular response to TBI, investigators have concluded that hippocampal neurogenesis may participate in cognitive recovery mechanisms after TBI using experimental strategies that inhibit neurogenesis response to injury.[202,207] However, another recent observation is that this altered neurogenic response to TBI may be short-lived and that, with chronic survival, numbers of newly formed neurons are reduced compared to control levels.[205,208] Recent studies have also indicated that the state of microglia activation could potentially play a major role in maintaining homeostasis of baseline neurogenesis in areas such as the SGZ of the hippocampus.[209] In the area of angiogenesis, data are also available indicating that anti-inflammatory M2 phenotype promotes angiogenesis whereas the proinflammatory M1 phenotype has antiangiogenic effects.[128] A greater understanding of the mechanisms controlling neurogenesis and angiogenesis after TBI and strategies to promote long-term repair mechanisms represent an important strategy for protecting the brain from progressive injury and long-term cognitive problems. In this regard, specific strategies, including exercise, motor rehabilitation, growth factor or hormonal, or other proneurogenic treatments, as well as therapeutic hypothermia, may enhance neurogenesis after brain injury.[206,210–213] Studies are critically evaluating mechanisms by which these various interventions can promote and sustain neurogenesis and whether these cellular events lead to chronic improvements in cognitive function after brain injury. The fact that neurogenesis occurs in the adult brain and can be negatively impacted by TBI emphasizes that these reparative processes represent extremely important targets for treating the progressive nature of TBI.

Cerebral Blood Flow Alterations

Early alterations in regional cerebral blood flow (rCBF) have been demonstrated in experimental and clinical models of TBI.[214–221] Immediately following TBI, significant changes in cerebral blood flow, as well as glucose metabolism, have been reported.[214,222–224] Reductions in blood flow are usually highly correlated with severity of injury, with trauma models showing reductions in rCBF

that do not reach ischemic levels.[225,226] However, after TBI, metabolic/hemodynamic requirements of the tissue may differ from normal tissues and could potentially participate in both the acute and more chronic consequences of neurotrauma.[227] In addition to alterations in blood flow, changes in vascular reactivity to various stimuli, including vasodilators, have also been emphasized in the literature.[228–231] Using a pial window model to evaluate vascular reactivity after TBI, researchers have reported that the vasodilatory characteristics of injured vessels are severely affected and may therefore participate in secondary injury mechanisms that include reduced hemodynamic needs to injured tissue.[228, 229] In human studies, stimulation-induced increases in blood flow have also been shown to be perturbed after TBI.[232–234]

Data are also available showing that, in addition to the acute changes in CBF, long-term alterations in rCBF are also observed in experimental and clinical models (Fig. 4).[233–241] Using MRI imaging or other methodologies, evidence for depressed blood flow throughout the injured and contralateral hemisphere have been documented. Moderate reductions in chronic blood flow can augment slow, evolving injury processes or aggravate events that were initiated by the acute insult. For example, inflammatory or excitotoxic processes could be aggravated by reduced blood flow. Strategies to improve blood flow include use of modifiers of vascular reactivity, such as nitric oxide or other strategies. The potential for cerebral emboli produced by the primary injury to occlude microvessels, abnormalities in coagulopathy, or whether microvascular vasospasm participates in reduced CBF needs to be addressed in future studies.[214,242,243]

Neurodegenerative Processes

Over the last several years, there has been an increased awareness that TBI can be an important risk factor for development of age-related neurodegenerative diseases, including AD and Parkinson's disease.[1,244] Clinical studies have emphasized that people with evidence of early TBI can show an increased incidence of neurodegenerative diseases.[10,11,245,246] Currently, the reason for this post-traumatic outcome is unknown, but recent data have implicated genetic factors and environmental as well as a variety of injury cascades, including prolonged inflammatory events, that may promote neurodegenerative processes. In several studies, evidence for focal protein aggregation, as well as abnormal accumulation of beta-amyloid precursor or tau protein, has been demonstrated in experimental as well as clinical specimens.[170,171,247–252] These patterns of abnormal protein accumulation occur in both GM and WM structures.[170,252,253] In a series of human brains obtained from individuals with repetitive mild concussions, increase tau ICC has been indicated as an ICC signature

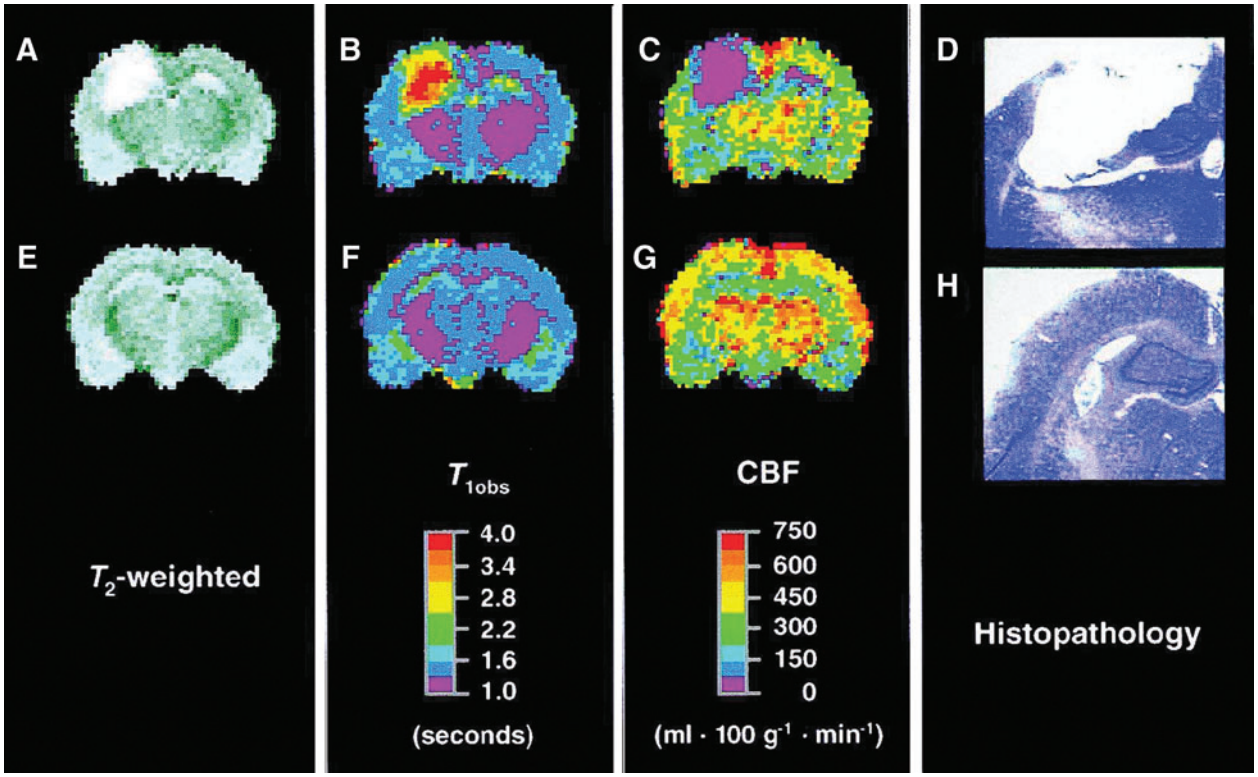

FIG. 4. Coronal brain magnetic resonance images and histopathology from rats at 1 year after controlled cortical impact (CCI; **A, B, C,** and **D**) and 1 year after sham surgery (**E, F, G,** and **H**). In the CCI example shown, a large cystic lesion was observed encompassing both the cortex and hippocampus ipsilateral to the impact at 1 year after injury. That lesion is identified as a region of hyperintensity on both the *T*2-weighted image (A) and the *T*1obs map (B) and as a region lacking perfusion (C). The corresponding histopathology (cresyl-violet–stained section through the imaging plane) confirms the location of the cystic cavity after CCI (D), but not after sham surgery (H). For figure presentation purposes, pixels outside the brain were assigned to zero intensity. Although the perfusion slice shown for injured rat (C) represents the best example of average for the overall effect of injury on CBF, it does not necessarily reflect the mean CBF for each individual region of interest. Reprinted from Kochanek and colleagues (2002), with kind permission of Mary Ann Liebert, Inc. CBF, cerebral blood flow.

for CTE.[254] Whether similar pathomechanisms involved in the progressive nature of TBI include CTE and other neurodegenerative disorders remain to be determined. However, it is important to emphasize that a spectrum of TBI severities as well as repetitive mild concussions appear to produce similar cellular responses to injury and therefore may include common pathomechanisms occurring in the more chronic stages of TBI.

Experimental and clinical research programs are targeting the devastating consequences of neurodegenerative diseases, including AD. Vaccine and antibody treatments are being tested to target abnormal protein aggregation and other neurodegenerative processes.[255–257] Whether or not therapeutic strategies that seem viable in TBI can also be used to reduce the more delayed and progressive pathophysiological cascades associated with neurodegenerative disorders is an area that needs to be emphasized in future research.

Summary

Both experimental and clinical evidence indicates the multifactorial nature of pathophysiological mechanisms that may underlie the progressive nature of TBI. Because the chronic consequences of TBI, including histopathological, physiological, and behavioral abnormalities, can be observed after mild, moderate, or severe injury, it may be difficult in the future to clarify whether any one dominant pathomechanism underlies the progressive nature of TBI. In addition, the acknowledgement of TBI being a possible risk factor for age-dependent neurodegenerative disease is also complicating the trauma field in terms of understanding pathophysiological events and treatment options. Hopefully, through genetic modeling approaches, combined with innovative cellular and functional approaches to evaluate novel pathomechanisms, a better understanding of how to best treat the chronic consequences of TBI will be achieved. Importantly, a greater understanding of the pathophysiological mechanisms associated with chronic TBI and the testing of novel therapeutic interventions using clinically relevant animal models will enhance the translation of new discoveries to the clinic.

Past attempts to translate postive pre-clinical findings targeting acute neuroprotection have been unsuccessful in terms of improving functional outcome.[258] However, lessons have been learned and strategies proposed on how best to approach the translation of pre-clinical data to the clinic. Specifically, several conditions, including independent data replication, the critical evaluation of the quality of research data, and clinical relevance are now emphasized in the neurotrauma literature.[259–261] Also, strategies that allow for data to be more easily shared among the scientific community have recently been published.[262] An increased emphasis of better communication between the laboratory and clinic in terms of designing trials and selecting treatments is also encouraged. It is anticipated that, in the future, pre-clinical findings will lead to successful clinical investigations potentially using novel combinatorial approaches, including neuroprotection, reparative approaches, and neurorehabilitation, to ultimately improve function in people living with the devastating consequences of TBI.

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Author Disclosure Statement

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