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Traumatic Brain Injury: A Disease Process, Not an Event

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Abstract

Traumatic brain injury (TBI) is seen by the insurance industry and many health care providers as an "event." Once treated and provided with a brief period of rehabilitation, the perception exists that patients with a TBI require little further treatment and face no lasting effects on the central nervous system or other organ systems. In fact, TBI is a chronic disease process, one that fits the World Health Organization definition as having one or more of the following characteristics: it is permanent, caused by non-reversible pathological alterations, requires special training of the patient for rehabilitation, and/or may require a long period of observation, supervision, or care. TBI increases long-term mortality and reduces life expectancy. It is associated with increased incidences of seizures, sleep disorders, neurodegenerative diseases, neuroendocrine dysregulation, and psychiatric diseases, as well as non-neurological disorders such as sexual dysfunction, bladder and bowel incontinence, and systemic metabolic dysregulation that may arise and/or persist for months to years post-injury. The purpose of this article is to encourage the classification of TBI as the beginning of an ongoing, perhaps lifelong process, that impacts multiple organ systems and may be disease causative and accelerative. Our intent is not to discourage patients with TBI or their families and caregivers, but rather to emphasize that TBI should be managed as a chronic disease and defined as such by health care and insurance providers. Furthermore, if the chronic nature of TBI is recognized by government and private funding agencies, research can be directed at discovering therapies that may interrupt the disease processes months or even years after the initiating event.

Key words: brain injury morbidity; chronic disease; head injury; head trauma; rehabilitation; traumatic brain injury

Introduction

The Funk and Wagnall's Standard Dictionary (Funk, 1980) defines an event as: "the final result; the outcome." Traumatic damage to the brain is seen by the insurance industry as well as many health care providers as an "event." Thus a broken brain is the equivalent of a broken bone—the final outcome of an insult to an isolated body system. Once "fixed," the brain requires no further treatment beyond a relatively brief period of rehabilitation, and there certainly will be no lasting effects on other organ systems. In contrast, the World Health Organization (WHO) defines a chronic disease as having one or more of the following characteristics: it is permanent, caused by non-reversible pathological alterations, requires special training of the patient for rehabilitation, and/or may require a long period of observation, supervision, or care (World Health Organization, 2002).

The purpose of this article is to encourage the classification of traumatic brain injury (TBI) as the beginning of a chronic disease process, rather than an event or final outcome. Head trauma is the beginning of an ongoing, perhaps lifelong, process that impacts multiple organ systems and may be disease causative and accelerative. Our intent is not to discourage patients with TBI or their families and caregivers, but rather to emphasize that TBI should managed as a chronic disease, and defined as such by health care and insurance providers. Furthermore, if the chronic nature of TBI is recognized by government and private funding agencies, research can be directed at discovering therapies that may interrupt the disease processes months or even years after the initiating event.

Post-Traumatic Mortality

Traumatic brain injury increases long-term mortality and reduces life expectancy (Table 1). In a 2004 study of mortality at 1 year post-injury among 2178 moderate to severe TBI patients, Harrison-Felix and associates reported that individuals with a TBI were twice as likely to die as a similar non-brain-injured cohort, and had a life expectancy reduction of 7 years (Harrison-Felix et al., 2004). A follow-up study on causes of death revealed that individuals surviving more than 1 year

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Table 1. Relationship between Traumatic Brain Injury and Mortality

n	*Increase in mortality*	*Cause of death*	*Reference*
1448	5.29 MRR, mod-sev 1.33 MRR, mild	Not stated	(Brown et al., 2004)
642	2.78 SMR	Not stated	(Ratcliff et al., 2005)
3679	7 times[a]	Not stated	(Selassie et al., 2005)
2140	37 times[a]	Seizures	(Harrison-Felix et al., 2006)
	12 times	Septicemia	
	4 times	Pneumonia	
	3 times	Respiratory disorders	
1678	49 times[a]	Aspiration pneumonia	(Harrison-Felix et al., 2009)
	22 times	Seizures	
	4 times	Pneumonia	
	3 times	Suicide	
	2.5 times	Digestive disorders	

[a]Greater than in a general population matched for age, race, and gender.
MRR, mortality risk ratio; mod-sev, moderate to severe TBI; SMR, standardized mortality ratio; TBI, traumatic brain injury.

post-injury were 37 times more likely to die from seizures, 12 times more likely to die from septicemia, 4 times more likely to die from pneumonia, and 3 times more likely to die from other respiratory conditions, than a matched cohort from the general population (Harrison-Felix et al., 2006). The greatest proportion of deaths (29%) was from circulatory problems. Although this number was not significantly greater than that of the general population, there was still a 34% increase over the expected number of circulatory-related deaths. In their most recent study, a retrospective analysis of charts from 1678 TBI patients admitted between 1961 and 2002, Harrison-Felix and colleagues observed that TBI patients were 49 times more likely to die of aspiration pneumonia, 22 times more likely to die of seizures, 3 times more likely to die of suicide, and 2.5 times more likely to die of digestive disorders than the general population matched for age, race, and gender (Harrison-Felix et al., 2009).

Shavelle and colleagues (Shavelle et al., 2001) reported that individuals with a TBI were three times more likely to die of circulatory conditions. Although it is somewhat intuitive that individuals with moderate to severe TBI would have a higher mortality rate than the general population, even individuals with mild TBI exhibited a small but statistically significant reduction in long-term survival (Brown et al., 2004).

Based on an examination of mortality among 3679 TBI patients within 1 year of discharge from acute care hospitals in South Carolina, Selassie and colleagues observed a sevenfold increased risk of death overall (standardized mortality ratio [SMR] = 7.1; 95% CI 6.3,7.9) within 15 months of discharge compared with the general U.S. population (Selassie et al., 2005). Patients treated at level 1 trauma centers were 44% (95% CI 0.4,0.8) less likely to die during the follow-up period than those treated at hospitals without a trauma center. Interestingly, patients with a TBI who were insured by Medicare were 1.6 times (95% CI 1.1,2.5) more likely to die than patients covered by commercial insurance.

In a retrospective cohort design study of 642 patients with a TBI discharged from a large rehabilitation hospital in the years 1974–1984, 1988, and 1989, Ratcliff and associates used a Poisson regression to estimate the ratio of the observed number of deaths to the expected number of deaths. The resulting SMR was 2.78 ($w^2 = 96.35$, $df = 1$, $p < 0.0001$), indicating more than a 2.5-fold increase in mortality rates in TBI patients (Ratcliff et al., 2005).

Brown and associates (Brown et al., 2004) conducted a population-based, retrospective, chart-review cohort study of 1448 TBI patients (164 moderate to severe and 1284 mild) from Olmsted County, Minnesota during the years 1985–2000. The mortality risk ratio (95% CI = 22.0–35.9) was 5.29 (range 4.11–6.71) in moderate to severe, and 1.33 (range 1.05–1.65) in mild TBI patients. This indicates that patients with mild TBI exhibited a small but statistically significant reduction in long-term survival compared to the general population. Considering the far greater numbers of mild than moderate to severe TBI patients, the increased mortality among patients with mild TBI would result in considerable numbers of TBI-related deaths.

Post-Traumatic Morbidity

Although many patients survive the initial insult, TBI initiates a chronic disease process that may ultimately contribute to their deaths months to years later.

Neurological disorders

Epilepsy. Traumatic brain injuries are a major cause of epilepsy, accounting for 5% of all epilepsy in the general population (Hauser et al., 1991; Table 2). Individuals with a TBI are 1.5–17 times (depending on the severity of the TBI) more likely than the general population to develop seizures (Annegers et al., 1998). Brain injury is the leading cause of epilepsy in the young adult population. Seizures were observed over a week after a penetrating TBI in 35–65% of individuals. In a study of 309 individuals with moderate to severe TBI followed as long as 24 years post-injury, 9% were being treated for epilepsy (Yasseen et al., 2008). In general, the risk of developing post-traumatic epilepsy (PTE) after a penetrating TBI is higher than after the most severe closed head injury. Englander and colleagues (Englander et al., 2003) studied risk factors for the development of PTE in 647 patients with moderate to severe TBI. The highest probabilities of PTE were seen in individuals with dural penetration by bone and metal, bi-parietal contusions, multiple intracranial operations, multiple subdural contusions, subdural hematoma requiring evacuation, and/or midline shift of >5 mm. As the time from

Table 2. Incidence of Subsequent Neurological and Neuroendocrine Disorders after Traumatic Brain Injury (TBI)

Disorder	n	*Incidence after TBI*	*Reference*
PTE	4541	Severe TBI: 16.7% Moderate TBI: 4.2%	(Annegers et al., 1998)
	137	13.1% late seizures in admitted patients	(Angeleri et al., 1999)
	490	25.3% late seizures in TBI rehab patients	(Asikainen et al., 1999)
	647	11% seizures within 2 years of TBI	(Englander et al., 2003)
SD	71	45% SD averaging 3 years	(Masel et al., 2001)
	87	46% SD; 23% OSA	(Castriotta et al., 2007)
	35	54% OSA; significantly worse performance on verbal and visual delayed recall and attention tests versus TBI patients without OSA	(Wilde et al., 2007)
PTH	100	35% severe GH deficiency in 21% of patients	(Aimaretti et al., 2004)
	70	33% at 3 months, 23% at 12 months	(Aimaretti et al., 2005)
	1137	27.5% in combined data from 19 studies	(Schneider et al., 2007a)

GH, growth hormone; OSA, obstructive sleep apnea; PTH, post-traumatic hypopituitarism; PTE, post-traumatic epilepsy; SD, sleep disorders.

injury to the time of the first post-TBI seizure may be as long as 12 years (Aarabi et al., 2000), there is need for heightened awareness of the development of epilepsy on the part of the patient, family, and treating medical personnel.

Sleep disorders. Sleep complaints are common following TBI. Subjective complaints of sleep disturbances have been reported in 70% of TBI outpatients (McLean et al., 1984). Disturbed sleep as measured by polysomnography was reported in 45% of a group of 71 individuals averaging 3 years post-injury (Masel et al., 2001).

There is an increased incidence of obstructive sleep apnea (OSA) in TBI patients (Castriotta et al., 2007). OSA is not only associated with decreased cognitive functioning (Wilde et al., 2007), but also with hemodynamic changes and severe cardiac arrhythmias during sleep. Such changes may be profound, with normotensive individuals developing systolic pressures approaching 300 mm Hg after apnea termination (Weiss et al., 1999). Even individuals with mild OSA have significant mortality risks (Partinen, 1988).

Neurodegenerative diseases

It is generally assumed that the cognitive gains made during the acute and post-acute period following TBI are maintained or may increase over the long term. There is a growing body of evidence, however, that suggests that a subset of individuals exhibits gradual declines in cognitive function after their injury (Tables 3 and 4). Till and colleagues (Till et al., 2008) performed serial neuropsychological assessments on 33 individuals with moderate to severe TBI over the first 5 years post-injury. Statistically significant cognitive declines on at least two neuropsychological measures were observed in 27.3% of subjects. Interestingly, the best predictor of

Table 3. Clinical Evidence of a Relationship between Traumatic Brain Injury (TBI) and Subsequent Neurodegenerative Diseases

Disease	*Effects of TBI*	*Reference*
AD, PD, LBD	Increased NF, BACE, APP, PS-1, α-syn, and Aβ levels in brain tissue samples from TBI patients	(Uryu et al., 2007)
PD	30–60% reduction in antioxidant glutathione and increased iron levels in the substantia nigra of PD patients	(Dunnett and Bjorklund, 1999)
PD	Odds ratio for PD after severe TBI = 11.0 ($p = 0.02$)	(Bower et al., 2003)
AD	Aβ present at autopsy in 30% of severe TBI patients	(Roberts et al., 1994)
AD	Aβ present in 30% of severe TBI patients as early as 2 hours	(Ikonomovic et al., 2004)
AD	Meta-analysis of 15 studies found that TBI is a risk factor for AD, but only in males	(Fleminger et al., 2003)

Aβ, amyloid-β; AD, Alzheimer's dementia; APP, amyloid precursor protein; α-syn, α-synuclein; BACE, β-site APP cleavage enzyme; LBD, Lewy body dementia; NF, neurofilament proteins; PD, Parkinson's disease; PS-1, presenilin 1.

Table 4. Experimental Evidence of a Relationship between Traumatic Brain Injury (TBI) and Subsequent Neurodegenerative Diseases

Animal	*TBI model*	*Neurodegenerative disease*	*Effects of TBI*	*Reference*
Mouse	CCI	MS, AD	Increased MMP expression; MMP KO led to reduced lesion volume, improved cognitive performance	(Wang et al., 2000)
Mouse	CCI	AD	Elevated Aβ levels and deposition impaired memory, increased lipid peroxidation	(Uryu et al., 2002)
Pig	RA	AD, PD	APP, Aβ, BACE, PS, and caspases-3 accumulation up to 6 months post-TBI	(Chen, 2004)
Rat	CCI	AD	Increased BACE-1 mRNA and protein expression and enzyme activity	(Blasko et al., 2004)
Rat	CCI	AD	Increased apolipoprotein D mRNA and protein expression	(Franz et al., 1999)
Rat	FPI	AD	Increased APP gene expression PID 2-7 days post-TBI; increased Aβ immunoreactivity and protein expression up to 1 year post-TBI	(Iwata et al., 2002)
Rat	FPI	AD	Increased APP in axons after TBI	(Bramlett and Dietrich, 2002)
Mouse	WDI	AD	Increased expression of PS and Nct in astrocytes and microglia after TBI	(Nadler et al., 2008)
Mouse	WDI	AD	Increased PS1 expression after TBI	(Cribbs et al., 1996)

Aβ, amyloid-β; AD, Alzheimer's dementia; APP, amyloid precursor protein; BACE, β-site APP cleavage enzyme; CCI, controlled cortical impact; FPI, fluid percussion injury; KO, knock-out; MMP, matrix metalloproteinase; MS, multiple sclerosis; Nct, nicastrin; PS-1, presenilin 1; RA, rotational acceleration; WDI, weight-drop injury.

decline was the amount of therapy received at 5 months post-injury. Those who received more therapy in the early post-injury months, regardless of severity of injury and level of neuropsychological impairment, were less likely to show declines over the long term. In its report on the Gulf War and Health, the Institute of Medicine concluded: "there is sufficient evidence of a relationship between sustaining a penetrating TBI and decline in neurocognitive function associated with the affected region of the brain and the volume of brain tissue lost" (Institute of Medicine, 2009). In addition, age is clearly a factor in long-term cognitive outcome after TBI. Older patients show a greater decline over the first 5 years following a TBI than younger patients (Marquez de la Plata et al., 2008)

Alzheimer's disease. Although the precise cause of Alzheimer's disease (AD) is unknown, numerous studies have shown that TBI may be a risk factor (Jellinger et al., 2001). In a large study of World War II veterans, Plassman and colleagues (Plassman et al., 2000) found that any history of brain injury more than doubled the risk of developing AD, as well as the chances of developing non-Alzheimer's dementia. They also observed that the worse the brain injury, the higher the risk for AD. Moderate brain injury was associated with a 2.3-fold increase in the risk, while severe head injury more than quadrupled the risk of the subsequent development of AD. Even individuals with no known cognitive impairments after TBI exhibited an increased risk of an earlier onset of AD (Schofield et al., 1997).

In their excellent review on this subject, Lye and Shores suggested many possible etiologies for this connection: damage to the blood–brain barrier causing leakage of plasma proteins into the brain, liberation of free oxygen radicals, and loss of brain reserve capacity, as well as the deposition of amyloid-β (Aβ) plaques (Lye and Shores, 2000).

Neurofilament proteins (NF), amyloid precursor protein (APP), β-site APP cleaving enzyme (BACE), presenilin-1 (PS-1), α-synuclein protein (α-syn), and Aβ were detected in brain tissue samples harvested 4 weeks after TBI (Uryu et al., 2007). Aβ plaques and neurofibrillary tangles comprised of tau protein are pathological characteristics of AD (Braak and Braak, 1991; Forman et al., 2004). BACE and PS-1 are critical components of the anabolic pathway that cleaves APP into Aβ (DeStrooper et al., 1998. Selkoe, 2001).

Iwata and associates reported increased expression of the APP gene, APP751/770, 2–7 days after fluid percussion TBI in rats (Iwata et al., 2002). Interestingly, Aβ immunoreactivity and protein expression increased for as long as a year post-injury, indicating that Aβ accumulation may continue long after APP gene expression returns to normal. Apolipoprotein D (ApoD) mRNA and protein expression were increased in the cortex and hippocampus of adult rats 2–14 days after concussion. ApoD may contribute to neurodegeneration in AD, since elevated ApoD levels have been observed in the CSF and hippocampus of AD patients (Terrisse et al., 1998).

Acute and chronic systemic inflammation/infections are associated with increases in serum tumor necrosis factor-α (TNF-α), resulting in a twofold increase in the rate of cognitive decline over a 6-month period in individuals with AD. Those with high baseline TNF-α levels had a fourfold increase in the rate of cognitive decline (Holmes et al., 2009).

Chronic traumatic encephalopathy. Chronic traumatic encephalopathy (CTE, aka "punch drunk" or dementia pugilistica) is a distinct neuropathological entity caused by repetitive blows to the head. CTE begins insidiously with

deterioration in concentration, attention, and memory, eventually affecting the pyramidal tract, resulting in disturbed coordination and gait, slurred speech, and tremors (McCrory et al., 2007). Although once thought to be a disease only seen in older retired boxers, the sporting world has recently been made aware of autopsy-confirmed findings of CTE in retired professional football players (Omalu et al., 2006). As repetitive head injuries occur in a wide variety of contact sports beginning at the junior high school level, there is clearly need for further study of this entity.

Parkinson's disease. Parkinson's disease (PD) has classically been characterized pathologically by the loss of neurons in the substantia nigra, leading to a selective loss of dopamine and its metabolites. Symptoms of PD include dementia, rigidity, tremor, postural instability, and slowness of movement (Dunnett and Bjorklund, 1999). Lewy bodies (concentric inclusion bodies in the neurons) are considered the histopathological signature of the disease (Zhang et al., 2000). Dopaminergic and noradrenergic neuronal loss have been observed in the locus caeruleus, as have Lewy bodies and neuronal loss in the cerebral cortex, anterior thalamus, hypothalamus, amygdala, and basal forebrain (Zhang et al., 2000).

Although the pathology of PD is well recognized, the mechanisms of neuronal death are uncertain. Experimental studies have implicated oxygen free radicals and oxidative stress (Zhang et al., 2000). α-Syn, which is implicated in other neurodegenerative diseases such as AD, may play a role in the development of PD after TBI (Bramlett and Dietrich, 2003). α-Syn immunoreactivity is a hallmark pathological finding in PD, Lewy body dementia, and multi-system atrophy (Norris et al., 2004; Smith et al., 2003). Increased brain tissue α-syn levels have been observed in brain tissue samples from TBI patients (Uryu et al., 2007). Other putative pathophysiological mechanisms of PD include endogenous and exogenous toxins, mitochondrial abnormalities (Rango et al., 2006), perturbations in the neuronal cytoskeleton and axonal transport, and calcium-induced injury, as well as apoptotic cell death (Dunnett and Bjorklund, 1999; Jenner and Olanow, 1998). Many of these mechanisms are thought to contribute to the pathophysiology of TBI (Bramlett and Dietrich, 2004)

Based on a study of 93 pairs of twins from a database of World War II veterans, Goldman and colleagues observed that if both twins had PD, the one with a TBI was more likely to have an earlier onset of the disease (Goldman et al., 2006). If only one twin had PD, that individual was more likely to have sustained a TBI. In a review of records of 196 PD patients from Olmstead County, Minnesota, Bower and colleagues observed an increased risk of PD in individuals who had sustained a TBI, a risk that increased with injury severity (Bower et al., 2003).

Neuroendocrine disorders

Post-traumatic hypopituitarism. TBI is associated with a host of neuroendocrine disorders, due perhaps to the induction of complex hormonal responses in the hypothalamic-pituitary-end-organ axes that ultimately lead to acute and/or chronic post-traumatic hypopituitarism (PTH). Hypopituitarism was reported in approximately 30% of moderate to severe TBI patients over the first year after injury (Schneider et al., 2007a). To date, studies on the relationship of PTH to mild TBI are lacking. In contrast to TBI patients who develop PTH that resolves over time, Aimaretti and colleagues reported that 5% of TBI patients studied had normal pituitary functioning at 3 months, but developed deficits a year post-injury, perhaps due to the loss of pituitary neuronal reserve (Aimaretti et al., 2005).

Although the underlying causes of PTH are unclear, vascular and structural changes to the hypothalamus, pituitary stalk, and the pituitary itself have been theorized (Edwards and Clark, 1986; Kelly et al., 2000). Current routine clinical imaging techniques may be inadequate for clearly visualizing structural pathology in the pituitary gland and tiny (2–3 mm in diameter) pituitary stalk. Normal imaging does not rule out the possibility of PTH (Agha et al., 2004; Schneider et al., 2007b)

Chronic PTH results in several related neuroendocrine conditions, including growth hormone (GH) and gonadotropin deficiencies and hypothyroidism. GH deficiency/insufficiency was found in approximately 20% of moderate to severe TBI patients (Agha and Thompson, 2006). GH deficiency (regardless of cause) was associated with an increased risk of fatigue, decreased exercise tolerance, depression, osteoporosis, hypercholesterolemia, and atherosclerosis, as well as a significant increase in mortality from vascular disease (Rosen and Bengtsson, 1990). Insulin-like growth factor-1 (IGF-1) is the major mediator of the actions of GH, and a low IGF-1 level is a hallmark of GH deficiency (Carro et al., 2002). In addition to enhancing neurogenesis and increasing neuronal excitability, IGF-1 enhances the clearance of Aβ from the brain (Carro et al., 2002).

Gonadotropin deficiency was observed in approximately 10–15% of individuals post-TBI (Agha and Thompson, 2006). Symptoms in adult males include decreased libido, muscle mass, and strength. A correlation has been found between low free testosterone levels and impaired cognitive function, although there is no clear consensus about testosterone supplementation therapy for cognition (Papaliagkas et al., 2008).

Hypothyroidism was found in approximately 5% of individuals post-TBI (Agha and Thompson, 2006). Associated signs and symptoms included weight gain, dyspnea, bradycardia, intellectual impairment (Agha and Thompson, 2006), hyperlipidemia, depression, hypothermia, and cold intolerance, as well as irregular menses and infertility (Garber and Bergmann Khoury, 2009). A recent study revealed a connection between hypothyroidism in females and the subsequent development of AD (Tan et al., 2008).

The need for monitoring for the development of PTH was emphatically stated in the 2009 Institute of Medicine report on the Gulf War: "That hormonal alterations substantially modify the posttraumatic clinical course and the success of therapy and rehabilitation underscores the need for the identification and appropriate timely management of hormone deficiencies to optimize patient recovery from head trauma, to improve quality of life, and to avoid the long-term adverse consequences of untreated hypopituitarism" (Institute of Medicine, 2009).

Psychiatric disease

In terms of impact on patients and their families and cost to society, psychiatric disorders are among the most important

Table 5. Relationship between Traumatic Brain Injury (TBI) and Psychiatric Disorders

Disorder	n	*Incidence after TBI*	*Reference*
Depression	722	42% MDD in 30-month study period	(Kreutzer et al., 2001)
	66	42% MDD in 1-year study period	(Jorge et al., 1993)
	100	48% MDD in 8-year study period	(Hibbard et al., 1998)
	666	27% MDD in 35.3-month study period	(Seel et al., 2003)
	1422	7.1% minor depression, 18.5% major depression	(Holsinger et al., 2002)
Psychotic disorder	750	7.5%, latency 15–19 years	(Achte et al., 1991)
	284	8.8%, latency 4.6 ± 4.4 years	(Fujii and Ahmed, 2001)
	60	6.7% in 30-year study period	(Koponen et al., 2002)
Substance abuse	60	11.7% alcohol abuse or dependence	(Koponen et al., 2002)
	361[a]	14%[b] alcohol abuse or dependence; 10.9% drug dependence	(Silver et al., 2001)
Suicide	361[a]	4.5 odds ratio for attempted suicide controlled for alcohol abuse	(Silver et al., 2001)
	145,440	3.02 suicide SMR for concussion 2.69 suicide SMR for fracture 4.05 suicide SMR for lesion[c]	(Teasdale and Engberg, 2001)
	39	33% considered at risk for suicide	(Leon-Carrion et al., 2001)

[a]5034 study subjects, 361 with TBI, 4673 without TBI

[b]24.5% alcohol abuse in TBI patients, 10.5% in control subjects (24.5–10.5 = 14%).

[c]SMR, standardized mortality ratio (observed suicides in study population/predicted suicides in a matched population); concussion, TBI without fracture or lesion; fracture, TBI with cranial fracture; lesion, TBI with contusion or traumatic intracranial hemorrhage.

MDD, major depressive disorder.

of the nation's health care issues. Current estimates in the U.S. suggest that the collective cost of psychiatric diseases could be as high as one-third of the total health care budget (Voshol et al., 2003). It is therefore critical to note that psychiatric and psychological deficits are among the most disabling consequences of TBI (Table 5). Many individuals with a mild TBI, and the majority of those who survive moderate to severe TBI, are left with significant long-term neurobehavioral sequelae.

In addition to the aggression, confusion, and agitation seen in the acute stages, TBI is associated with an increased risk of developing numerous psychiatric diseases, including obsessive-compulsive disorder, anxiety disorders, psychotic disorders, mood disorders, and major depression (Fleminger, 2008; Zasler et al., 2007), as well as substance abuse or dependence (Hibbard et al., 1998; Holsinger et al., 2002; Koponen et al., 2002; Silver et al., 2001). TBI is associated with high rates of suicidal ideation (Kishi et al., 2001; Leon-Carrion et al., 2001), attempted suicide (Silver et al., 2001), and completed suicide (Teasdale and Enberg, 2001). In chronic TBI, the incidence of psychosis is 20%. The prevalence in TBI patients was 18–61% for depression, 1–22% for mania, 3–59% for post-traumatic stress disorder, and 20–40% for post-traumatic aggression (Kim et al., 2007).

In a study of 60 patients with TBI followed for up to 30 years post-injury, Koponen and colleagues observed that 50% developed a major mental disorder that began after their TBI (Koponen et al., 2002). In a long-term follow-up study of 254 individuals at 2 and 5 years post-TBI, it was found that there was a higher incidence of cognitive, behavioral, and emotional changes at 5 years than at 2 years post-TBI (Olver et al., 1996). Thirty-two percent of those working at 2 years were unemployed at 5 years. Thus in many patients TBI results in long-term or perhaps permanent vulnerability to psychiatric illness.

This lasting susceptibility to psychiatric disorders may be especially prominent in children, perhaps due to frequent damage to pre-frontal brain structures (Anderson et al., 1999). Many functions subserved by the frontal lobes are more severely affected if the injury occurs in the early childhood years (Anderson et al., 1999). Moreover, as opposed to the anticipated improvement in behavior and cognitive functioning that normally occurs as a child matures, young children who have sustained a TBI tend to worsen over time. Even mild TBI in childhood may lead to psychiatric issues in adolescence and early adulthood. McKinlay and colleagues, who followed 1000 infants in New Zealand from birth, reported that children who required overnight hospitalization due to mild TBI showed no academic or cognitive differences from the uninjured cohort before age 10 (McKinlay et al., 2002). However, by ages 10–13 this group showed an increase in conduct disorder, oppositional-defiant disorder, and attention-deficit hyperactivity disorder.

Non-neurological disorders

Sexual dysfunction. Sexuality, both physiological and functional, plays an enormous role in our lives. Sexual dysfunction is an important issue in the general population, and is a major ongoing problem in the TBI population. Between 40 and 60% of TBI patients complain of sexual dysfunction (Zasler et al., 2007). As noted previously, transient hypogonadism is common acutely following TBI, yet it persists in 10–17% of long-term survivors (Agha and Thompson, 2005). Beyond just the fertility and psychosocial issues presented by hypogonadism, muscle weakness and osteoporosis may have a significant impact on long-term function and health, with the consequences exacerbated by prolonged immobility following a TBI (Agha and Thompson, 2005).

Incontinence. One of the most frequent and psychologically devastating consequences of TBI is bladder and bowel incontinence. Brain injury frequently affects the cerebral

structures that control bladder storage and emptying functions, resulting in a neurogenic bladder. Based on a review of the records of over 1000 TBI patients, Foxx-Orenstein and colleagues observed that one-third were incontinent of bowel at admission, 12% at discharge, and 5% at 1 year post-TBI (Foxx-Orenstein et al., 2003). In their review of medical complications in 116 individuals with moderate to severe TBI, Safaz and colleagues found that 14% had fecal incontinence at over 1 year post-injury (Safaz et al., 2008). Fecal incontinence is not only socially devastating, but it may contribute to skin breakdown, decubitus ulcers, and skin infections (Foxx-Orenstein et al., 2003).

Urinary incontinence is an enormous social and medical problem. Chua and associates reviewed the records of 84 patients admitted to a rehabilitation unit within 6 weeks of injury and observed that 62% reported urinary incontinence (Chua et al., 2003). This improved to 36% at discharge; however, 18% remained incontinent at 6 months. Safaz and colleagues found urinary incontinence in 14% of their cohort over a year post-injury (Safaz et al., 2008). Urinary incontinence is associated with the development of frequent urinary tract infections and decubitus ulcers.

Musculoskeletal dysfunction. Spasticity, a common problem after moderate to severe TBI, is characterized by increased muscle tone that results in abnormal motor patterns that may interfere with general functioning, and limit self-care, mobility, and independence in the activities of daily living (Elovic et al., 2004). Untreated, it will eventually lead to muscle contractures, tissue breakdown, and skin ulceration (Zafonte et al., 2004).

The incidence of fractures in TBI is approximately 30%. TBI patients with fractures, especially fractures of the long bones, are at risk for heterotopic ossification (HO), which may develop as late as 3 months post-injury. HO is defined as "the development of new bone formation in soft tissue planes surrounding neurologically affected joints," and has in incidence of 10–20% following TBI (State of Colorado Department of Labor and Employment, 2006). This ectopic bone formation may eventually lead to limited joint mobility, pain, increased spasticity, neurovascular entrapment, and pressure ulcers. Safaz and colleagues found HO in 17% of their cohort over a year post-injury (Safaz et al., 2008). Brain injury severity and autonomic dysregulation accurately predict HO in patients with TBI (Hendricks et al., 2007).

One explanation for the development of HO is that osteoblasts (the pluripotent mesenchymal cells responsible for bone formation) undergo inappropriate differentiation within muscles. Prostaglandins normally help regulate osteoclast and osteoblast function, and it has been suggested that prostaglandin dysregulation after TBI may be a factor in the development of HO (Vanden Bossche and Vanderstraeten, 2005). The mechanism behind increased post-traumatic osteogenesis is not fully understood; however, it is clear that there are unknown centrally-released osteogenic factors that that enter into the systemic circulation following brain injury (Toffoli et al., 2008).

Metabolic dysfunction. A TBI appears to impact the way the body absorbs, utilizes, and converts amino acids. Amino acids play a critical role in brain function because they are incorporated into functional and structural proteins, and are the precursors of neurotransmitters involved in cognitive, motor, neuroendocrine, and behavioral functions. Aquilani and colleagues found significant plasma amino acid abnormalities in individuals with an acute (30–75 days) TBI (Aquilani et al., 2000). All the essential amino acids (EAA, those that cannot be synthesized by the body), and 50% of the non-essential amino acids (NEAA, those that can be synthesized by the body), were significantly lower in individuals with brain injuries than in controls. The same group also found that significant abnormalities at admission were essentially unchanged upon discharge. Most notable was a reduction in tyrosine, a NEAA precursor to serotonin (Aquilani et al., 2003).

Although the amino acid abnormalities in the acute and subacute phases of TBI could be due in part to muscle tissue depletion, hypercatabolic states, and inadequate nutritional supply, Borsheim and associates found significant abnormalities in plasma EAA and NEAA concentrations in chronic moderate to severe TBI patients (Borsheim et al., 2007). Compared to controls, TBI patients (17 ± 4 months post-injury) consuming a 2000-cal/d dietician-approved diet were found to have significantly lower plasma levels of the EAA valine. Valine competes with tryptophan for the same transporter system into the brain, and low valine levels will increase tryptophan concentrations in the brain (Borsheim et al., 2007). As tryptophan is a precursor to serotonin, an increase in tryptophan may increase serotonin production and consequently increase central fatigue.

When administered a drink containing 7 g of EAA, patients with TBI had significantly lower plasma levels of NEAA and valine than control subjects. The NEAA with the smallest increases in the TBI group were alanine and glutamine, which is a precursor to the excitatory neurotransmitter glutamate. Remarkably, TBI patients who were eating a normal diet and were partially back into society and performing activities of daily living, still exhibited abnormalities in plasma amino acids more than 1.5 years post-injury (Borsheim et al., 2007). Glutamine concentrations were reduced by 14% in temporal lobe biopsies in patients with AD, suggesting a glutaminergic cause for the decline in memory and learning seen in that disease (Francis et al., 1993). Moreover, abnormalities in amino acid metabolism may contribute to some of the symptoms (fatigue, decreased memory, and poor learning) seen in patients with TBI.

Etiology

Traumatic central nervous system injury often results in chronic disability with lasting cognitive and motor disorders (Levin et al., 1987). However, what remains uncertain is whether chronic damage is due to long-term consequences of the initial traumatic insult (i.e., Wallerian degeneration) (Adams et al., 2000; Graham et al., 1995), or progressive secondary injury (Bramlett and Dietrich, 2002; Bramlett et al. 1997; Dixon et al., 1999; Smith et al., 1997). Ng and associates (Ng et al., 2008) used MRI to evaluate 14 patients 4.5 months and 29 months post-moderate to severe TBI. In 10 individuals the MRIs showed progression of encephalomalacia. Greenberg and colleagues (Greenberg et al., 2008) studied a similar cohort of 13 patients 4.5 months and 29 months following moderate to severe TBI using diffusion tensor imaging. The studies showed subacute white-matter injury progression in

the frontal and temporal lobes bilaterally. Clinical (Anderson and Bigler, 1995) and experimental (Bramlett and Dietrich, 2002; Dixon et al., 1999; Smith et al., 1997) research has demonstrated progressive CNS atrophy after TBI. Anderson and Bigler (1995) reported widespread white- and gray-matter atrophy in TBI patients, and observed that the extent of ventricular expansion positively correlated with severe memory deficits. Furthermore, dilation of the anterior horn of the lateral ventricle was associated with atrophy of the corpus callosum (Anderson and Bigler, 1995). MRI images recorded as long as 603 days after TBI revealed significant atrophy of the anterior hippocampus. Interestingly, the atrophy involved both anterior hippocampal regions, regardless of the location of the primary injury (Ariza et al., 2006). A positive correlation between cognitive outcome and extent of brain atrophy has been observed in other studies of the chronic effects of TBI (Cullum and Bigler, 1986; Reider-Groswasser et al., 1993).

These studies suggest that the progression of symptoms seen in chronic TBI is due in part to defective apoptotic rather than necrotic cell death mechanisms. Genetic changes affecting cellular demise by apoptosis has also been proposed as a mechanism in delayed radiation vasculopathy syndrome (O'Connor and Mayberg, 2000).

The mechanisms by which a brain injury can impact other organs is not known, but clearly there is an indirect effect. Mirzayan and colleagues (Mirzayan et al., 2008) subjected mice to a controlled cortical impact brain injury and sacrificed them at 96 h. Histopathological changes were found in the liver and lung, suggesting that an isolated TBI can lead to the migration of immune incompetent cells to the peripheral organs, thus potentially leading to their dysfunction. The immune response is significantly impaired acutely following TBI ("post-traumatic immune paralysis"), and may be associated with the high prevalence of infections seen in TBI patients (Kox et al., 2008).

Polio and subsequent post-polio syndrome (PPS) may well serve as a model for chronic post-traumatic disease (CPD). A 1987 National Health Interview Survey estimated that after a period of neurological and functional stability, of the 640,000 survivors of polio surveyed, approximately half had new late manifestations of the disease, with an average latency of 35 years. Weakness and fatigue were the most common symptoms (Jubelt et al., 1999).

In the PPS patient, the terminal axons of the surviving motor neurons sprouted in an attempt to reinnervate muscle fibers that had lost innervation from non-surviving motor neurons (Dalakas 1995). The phenomenon can be captured by single-fiber EMG measuring increased jitter in these patients (Jubelt and Agre, 2000). Jitter measures the time difference of the depolarization of two muscle fiber potentials within the same motor unit upon successive firings. Jitter increases after an attack of polio and persists indefinitely, suggesting ongoing denervation and reinnervation (Jubelt et al., 1999). Although the jitter in the axons of the peripheral nervous system cannot be measured within the axons of the brain, the concept of ongoing denervation and reinnervation within those axons certainly remains a possible explanation for the varying symptomatology displayed over time by individuals with TBI. This "impaired transmission model" may partly explain why some individuals with TBI have benefited from anticholinesterase medications (Silver et al., 2006). This ongoing process of denervation and reinnervation can be stressing to the neuronal cell bodies, that may not be able to keep up with the required metabolic demands, causing them to fail. It is certainly possible that "injured" neurons may have a shorter-than-normal lifespan, and may succumb earlier to the normal aging process (Dalakas, 1995).

Discussion

Historically, individuals living with a brain injury have been referred to as brain injury "survivors." Perhaps the concept of merely "staying alive" was used, because as few as 30 years ago the majority of individuals with a moderate to severe TBI succumbed soon after their injury. Perhaps it was used to imply that the individual "outlived" their injury and persevered despite the hardship of the trauma.

This term, however, does not address the reality of brain injury. Cancer survivors are believed to be cured; they have outlived their disease. Many individuals who sustain a TBI recover completely; they have truly survived their injury. However, annually in the United States alone, over 90,000 TBI patients become disabled (Thurman et al., 1999). In this article we have discussed only a small percentage of the causes of TBI-induced disability and the ongoing and developing medical conditions faced by TBI patients and their families. Presently, well over 3.5 million individuals in the U.S. are disabled due to the myriad sequelae of TBI (Zaloshnja et al., 2008). Brain trauma has resulted in a condition that may be disease-causative and disease-accelerative. As a result of their brain trauma, those 3.5 million Americans now have a lifelong condition that might be termed "chronic traumatic brain injury disease." Certainly by suggesting that a TBI should be approached differently than in the past, the authors do not wish to appear to depersonalize the individual with this disease. Rather, we would hope to achieve one of the goals of chronic disease management: to develop "expert patients" (Tattersall, 2002), who truly understand their disease and can therefore take steps to mitigate all the medical issues that develop after a TBI. The goal is to treat the patient with the disease, as opposed to merely treating the disease in the patient.

Chronic traumatic brain injury disease should be reimbursed and managed on a par with all other chronic diseases. Only then will the individuals with this condition get the medical surveillance, support, and treatment they so richly deserve. Only then will brain-injury research receive the funding it requires. Only then will we be able to truly talk about a cure.

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