Rehabilitation of Moderate-to-Severe Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force. Traumatic brain injury is a leading cause of morbidity and disability and is considered a major public health concern. Traumatic brain injury sequelae can lead to long-term impairments in physical, cognitive, behavioral, and social function. Traumatic brain injury rehabilitation requires an interdisciplinary holistic team approach in the management of medical complications, the prevention of further disability, and helping patients return to their highest level of independence. The authors review TBI pathophysiology, grading severity, common medical complications, cognitive rehabilitation, prognosis, and common outcomes used in TBI rehabilitation.

Keywords
- rehabilitation
- disability
- cognitive rehab
- severe brain injury

Traumatic brain injury (TBI) is a leading cause of morbidity, morality, and long-term disability in the United States and is considered a major public health concern with significant socioeconomic impact.[1–3] The Centers for Disease Control estimates the annual incidence of TBI at 1.7 million—which includes over 1.365 million emergency rooms visits, 250,000 hospitalizations, and 52,000 deaths—with an annual total cost-of-care (direct and indirect) ranging between $48 to 76 billion.[4–6] The Department of Defense reports over 303,700 cases since 2000 with over 30,000 moderate, severe, or penetrating brain injuries.[7] However, these may be conservative estimates given modest reporting, individuals not seeking medical attention, treatment in the primary care setting, and the variability in the definition of TBI.[8–10] Recent studies show that over 40% of persons discharged after acute TBI hospitalizations develop long-term disability with prevalence rates ranging from 3.3 to 5.3 million, the majority of which are associated with moderate to severe TBI.[1,2,11] Moderate-to-severe TBIs often co-occur with polytraumatic injuries including multiorgan injury, fractures, burns, or amputations.[12] The range of comorbid conditions and variations in brain injury itself leads to an array of physical, cognitive, behavioral, and psychosocial impairments, with outcomes ranging from complete recovery to permanent disability or death.[1]

Definition and Pathophysiology

Traumatic brain injury is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force with new onset or worsening of at least one of the following: decreased level of consciousness, memory loss for events before or after injury, alteration of mental status, neurologic deficits, or an intracranial lesion.[13,14] The pathophysiology of TBI can be separated into primary injury and resultant secondary injury. The primary injury occurs at the

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time of initial impact from an external force such as a direct mechanical force, acceleration–deceleration forces, penetrating objects, or blast waves. Secondary injury can occur from seconds to weeks after the primary injury and is associated with impairments of cerebral blood flow and metabolism, hypoxia, edema, and a cascade of neurochemical changes due to release of excitotoxic neurotransmitters.[15] The immediate management is focused on medical stabilization through the use of advanced trauma life support protocols that minimize secondary injury by controlling intracranial hypertension, maintaining oxygenation, and promoting ionic homeostasis to minimize cellular injury through nonsurgical (e.g., osmotherapy, hyperventilation, hypothermia, body rotation with head of the bed raised to 30 degrees and adjusted head posture to neutral) and surgical (e.g., cerebrospinal fluid drainage, decompressive craniectomy) interventions.[15–17] Prevention of secondary injury and comorbid medical complications is paramount in improving long-term outcomes and disability.

Severity Grading of Traumatic Brain Injury

The injury severity of a TBI ranges from mild (sports concussion) to severe (disorders of consciousness) in nature (►**Table 1**). Severity is most often classified based on the Glasgow Coma Scale (GCS) score, length of loss of consciousness (LOC), or length of posttraumatic amnesia (PTA), or some combination of the three. The GCS is a brief measure of altered consciousness that assesses vision, and motor and verbal responses, with a total score that ranges from 3 to 15. A GCS score of 3 to 8 indicates severe TBI, 9 to 12 is moderate TBI, and a GCS of 13 to 15 is mild TBI.[18] A LOC lasting 0 to 30 minutes denotes mild TBI, 30 minutes to 24 hours denotes moderate TBI, and more than 24 hours indicates severe TBI. Posttraumatic amnesia is the impaired recall of events surrounding the injury with either retrograde PTA (impaired recollection of events immediately preceding the injury) or anterograde PTA (deficit in forming new memories after the injury).[19] Anterograde PTA lasting up to 1 day is considered mild TBI, PTA lasting more than 1 day and less than 7 days is considered moderate TBI, and PTA lasting more than 7 days is considered severe TBI. Currently, there are no cognitive or pharmacological treatments known to reduce PTA duration. Increased PTA duration can be an indicator of poor functional outcome and prognosis.[20,21]

Role of Structural Neuroimaging in Acute Management of TBI

Noncontrast head computed tomography (CT) is used in the acute management of TBI to determine lesion severity and progression (particularly for epidural and subdural hematomas, subarachnoid and intraparenchymal hemorrhage, herniation, and contusion), the need for intracranial pressure monitoring, and the necessity of neurosurgical intervention. A noncontrast head CT is routinely indicated in patients who meet clinical criteria for a moderate or severe TBI or in cases of suspected complicated mild TBI. Complicated mild TBI occurs when the patient's GCS is greater than 13, but the patient has intracranial lesions evident on day-of-injury imaging. Identifying complicated mild TBI is important because a growing body of research indicates that cognitive and functional outcomes may be similar for patients with moderate TBI and those with complicated mild TBI.[22,23] The American College of Emergency Physicians (ACEP)/Centers for Disease Control and Prevention provide decision-making guidelines for determining when a CT should be considered to rule out complicated mild TBI.[24] Even when no LOC or PTA has occurred, the guidelines suggest a head CT when one of the following is present: focal neurologic deficit, physical signs of basilar skull fracture, coagulopathy, GCS less than 15, dangerous mechanism of injury (defined as ejection from a motor vehicle, pedestrian struck by a motor vehicle, fall from more than 3 feet), or age greater than 65. If LOC or PTA has occurred, then a head CT is recommended in mild TBI if any of the above is observed or if one of the following is present: posttraumatic seizures (PTSs), deficits in immediate learning or memory, physical evidence of trauma above the clavicle, headache, drug or alcohol intoxication, or age greater than 60. The necessity of follow-up CT hours after the initial scan is often determined by initial GCS score, change in status over serial clinical exams, presence of coagulopathy, and severity of initial CT findings.[25]

Magnetic resonance imaging (MRI) is very rarely used to obtain initial imaging in acute TBI due to limited availability and longer image acquisition times relative to CT. Nonetheless, follow-up MRI can be helpful in clarifying the characteristics of focal neurologic damage identified on CT and has been shown to be more sensitive to small extra-axial fluid collections and cortical contusions.[26] Additionally, MRI is helpful for determining the age of various lesions in patients

Table 1 Severity classification of traumatic brain injury

Criteria	Mild	Moderate	Severe
Glasgow Coma Scale (GCS best within 24 h)	13–15	9–12	3–8
Loss of consciousness (LOC)	0–30 min	31 min to 24 h	> 24 h
Alteration of consciousness (AOC)	Up to 24 h	> 24 h Severity based on other criteria	> 24 Severity based on other criteria
Posttraumatic amnesia (PTA)	0–1 d	>1 d to < 7 d	> 7 d
Structural neuroimaging	Normal	Normal or abnormal	Normal or Abnormal

Source: Adapted from the VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury[13]

who have a history of prior head trauma.[25] A growing body of evidence also suggests that MRI may be particularly sensitive to chronic parenchymal changes and apoptosis in TBI. For instance, Green and colleagues examined chronic changes in ventricle-to-brain ratio, the left and right hippocampus, and the corpus callosum in a sample of predominantly severe TBI patients.[27] When compared with a small sample of healthy controls over the course of 15 months, 96% of patients had atrophy (defined as change in volume greater than 2 standard deviations) in at least one structure, and 75% showed decline in at least three of the four regions. In addition to conventional MRI sequences, evidence is emerging that new techniques are able to improve detection of lesions and their relationship to outcomes. Such methods include diffusion tensor imaging (DTI), voxel-based morphometry (VBM), and automated quantitative image analysis.[25] Diffusion tensor imaging is particularly promising for imaging acute traumatic axonal injury (TAI) across all levels of TBI severity, which is currently poorly visualized in conventional MRI sequences. The advantage of DTI is its ability to characterize damage to white matter pathways through the quantification of intraparenchymal water diffusion by measuring fractional anisotropy.[28] Although DTI is primarily used in research settings, its utility in clinical practice may grow as its research base grows, and it continues to demonstrate robust correlations to medical, cognitive, behavioral, and functional outcomes.

Interdisciplinary Rehabilitation Team

The constellation of impairments in postacute brain injury patients requires a comprehensive and individualized rehabilitation program based on a thorough interdisciplinary team (IDT) evaluation. The IDT is a collaborative team composed of physicians, neuropsychologists, rehabilitation and clinical psychologists, speech and language pathologists, physical therapists, occupational therapists, low vision therapists, recreational therapists, case managers, dieticians, chaplains, and wound-care providers. The IDT model also assumes the family and patient are the most integral part of the team.[29] The main goal of the IDT is to return the patient to his or her highest functional level by maximizing health and independence. The rehabilitation process plays a significant role in the TBI survivor's long-term quality of life; early intensive rehabilitation has been shown to improve long-term functional outcomes while decreasing LOS and total cost of care.[30–32]

Medical Complications: Evaluation and Management

Initial evaluation and management of any TBI patient should begin with a comprehensive history and physical exam by a trained brain injury medicine physiatrist. There are a plethora of postacute medical complications, which can manifest after moderate-to-severe TBI. The mainstay of treatment should be to minimize any further impairment and to optimize functional outcomes.

Disorder of Consciousness

Severe TBI can result in a prolonged period of impaired consciousness. Disorders of consciousness (DOC) can be broadly categorized into three stages: coma, vegetative state (VS), and the minimally conscious state (MCS).[33] Coma is a state of pathological unconsciousness in which there is no grossly observable evidence of purposeful movement, sleep–wake cycles, or eye opening. Patients who progress from a coma usually enter a VS that is characterized by spontaneous eye opening and evidence of wakefulness or sleep–wake cycles, but no purposeful or behavioral awareness of self or the environment. The VS is often referred to as the "condition of wakeful unconsciousness."[34] The MCS follows the VS, and is defined as a state of severely altered consciousness with definite evidence of awareness of self or environment through simple command following, purposeful movements, or appropriate emotional responses to an external stimulus. An individual is considered "emerged" from a MCS when there is consistent demonstration of functional communication (verbalization, written yes/no, or use of a augmentative assisted device) and functional object use (two objects on two separate evaluations).[33] Based on the American Congress of Rehabilitation Medicine's review of multiple DOC assessments, the Coma Recovery Scale-Revised (CRS-R) is currently the recommended measure for monitoring patients' progression among the levels of consciousness.[35] The CRS-R is a 23-item scale comprising six subscales addressing visual, auditory, motor, oromotor, communication, and arousal categories; it has demonstrated its validity in the prognostic assessment, treatment planning, and differential diagnosis in patients with DOC.[36] Pharmacological and nonpharmacological interventions in patients with DOC has been aimed at improving wakefulness and arousal. Giacino et al in a double-blind, randomized, placebo controlled study showed amantadine accelerated functional recovery in patients with post-traumatic DOC.[37] Other interventions such as zolpidem and methylphenidate, as well as an implantable deep brain stimulator and multimodal sensory stimulation program have shown limited improvement in patients with DOC.[38–40] The mainstay of medical management should be focused on the prevention of a secondary medical complication and minimizing further impairment and disability.

Cranial Nerve Injury

Injuries to the cranial nerves are common in TBI. Because they traverse many intracranial bony prominences, they are susceptible to mechanical forces that cause injury. The true incidence of cranial nerve injuries is difficult to estimate and varies among studies. In general, the olfactory nerve is the most often injured and one of the least tested, followed by the facial and vestibulocochlear nerve. Cranial nerves 9 to 12 are usually the least commonly injured. The facial nerve has the best chance for recovery with the least likely being the olfactory, optic, and vestibulocochlear nerves. Treatment is typically symptom-based, and studies show mixed results as

to the benefit of steroids or surgical decompression of the optic or facial nerves.[41]

Posttraumatic Hydrocephalus

Hydrocephalus is defined as "an active distention of the ventricular system of the brain related to inadequate passage of CSF from its point of production within the ventricular system to its point of absorption in the systemic circulation."[42] Posttraumatic hydrocephalus (PTH) is the most common treatable neurosurgical complication during rehabilitation of TBI.[43] The incidence of PTH is broad, with studies reporting between less than 1% up to 45% in patients with severe TBI.[44] This broad range may be partially explained by the lack of definitive diagnostic criteria and the difficulty in deciphering hydrocephalus from central atrophy or ex vacuo ventricular dilation. In 2008, Tian et al reviewed the incidence of PTH in patients with traumatic subarachnoid hemorrhage (SAH). Approximately 12% of patients with traumatic SAH developed PTH within 3 months, with the majority occurring in 2 to 4 weeks.[45]

Hydrocephalus can be divided into two types: communicating and noncommunicating.[42,43] In communicating hydrocephalus, the different portions of the ventricular system are interconnected and fluid may flow from the ventricular system to the subarachnoid space. Communicating hydrocephalus is the most frequent type seen in TBI with blood products or fibrosis impeding the cerebrospinal fluid (CSF) flow into the bloodstream through the arachnoid granulations.[42] This may also present as what is known as normal pressure hydrocephalus (NPH). In noncommunicating, or obstructive hydrocephalus, CSF flow is blocked from passing between the ventricles or exiting the ventricular system.

Risk factors for PTH include intracranial hemorrhage (particularly intraventricular hemorrhage), SAH, meningitis, the use of postdecompressive craniectomy, the duration of coma, and advanced age of the patient.[44] Early signs and symptoms of hydrocephalus can include manifestations of increased intracranial pressure such as nausea, vomiting, lethargy, headaches, altered mental status, gait disturbances, and papilledema. The constellation of signs known as the Cushing triad of hypertension, bradycardia, and hypoventilation can also be seen. Normal pressure hydrocephalus typically presents with the clinical triad of gait ataxia, urinary incontinence, and dementia, with gait impairment the most likely to respond to treatment. The cognitive abnormalities are more likely to include poor activity initiation, psychomotor slowing, decreased attention, and forgetfulness. Gait abnormalities often present as shuffling or short-stepping.[46,47]

The definitive treatment for hydrocephalus usually requires the placement of a shunt. Temporary measures may include the use of diuretics (furosemide, mannitol), osmotic agents (glycerol, acetazolamide), or serial lumbar punctures. Ventriculoperitoneal shunts are used most commonly for posttraumatic hydrocephalus. Most patients who receive shunt placement improve clinically and radiographically. On the contrary, untreated PTH can lead to worsening of the aforementioned signs and symptoms as well as alterations in consciousness, behavior, and global cognitive dysfunction.[44,45]

Paroxysmal Sympathetic Hyperactivity

Paroxysmal sympathetic hyperactivity (PSH) is a recurrent and episodic syndrome that can be seen in several types of acquired brain injury. The predominant clinical manifestations of PSH include hypertension, tachycardia, hyperthermia, diaphoresis, and hyperthermia. These can also be observed with motor features of increased spasticity, dystonia, and extension or flexion posturing.[48] These symptoms may be an exaggerated response to some noxious external stimuli, such as sedation withdrawal, endotracheal tube suctioning, passive movement or repositioning, urinary retention, constipation, or loud irritating noises. A review article by Perkes et al identified a spectrum of additional negative prognostic consequences for increased sympathetic tone that include hypermetabolism leading to weight loss, prolonged hospital stay, increased likelihood for tracheostomy, worse outcome by Functional Independence Measure (FIM) scoring, increased duration of posttraumatic amnesia, cardiac dysfunction, immune suppression, and increased incidence of heterotopic ossification.[49]

The majority of PSH cases are from TBI (79.4%), followed by hypoxic brain injury (9.7%) and stroke (5.4%).[49] Paroxysmal sympathetic hyperactivity has been identified using multiple terms including dysautonomia, episodic autonomic instability, central autonomic dysfunction, sympathetic storm, diencephalic seizures, autonomic dysfunction syndrome, and paroxysmal autonomic instability with dystonia.[49] Another review by Perkes et al in 2011 reported estimates of PSH to occur in 8 to 33% of TBI patients, but the lack of standardized diagnostic criteria for PSH as well as the use of multiple terms to describe this syndrome has likely led to an underreporting and wide variation in incidence in the current literature.[50] In their article, they identified 81 papers whose authors presented case reports or literature reviews of PSH after acquired brain injury. Only 33% of these studies utilized some type of diagnostic criteria—of which nine separate novel or substantially modified diagnostic criteria sets were analyzed. Although these sets showed agreement on clinical features such as heart rate, blood pressure, respiratory rate, temperature,diaphoresis, and motor hyperactivity, Perkes et al highlighted a lack of diagnostic uniformity. Further impeding the formalization of standardized diagnostic criteria is the overlap that excessive sympathetic activity can have with other disorders in critically ill patients, such as infections, seizures, hydrocephalus, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, medication withdrawal, autonomic dysreflexia in concurrent spinal cord injury, acute coronary syndrome, and pulmonary embolism. Therefore, even though there may be some consensus on some of the primary signs and symptoms of PSH, the number, length, frequency and severity of these has differed across studies.[48,50]

Posttraumatic Agitation

Posttraumatic agitation has been defined as a subtype of delirium during PTA with behaviors such as aggression, disinhibition, and/or emotional lability occurring in 35 to 96% of patients during the acute phases of brain injury recovery.[51–53] Posttraumatic agitation can occur during the initial stages of neurobehavioral recovery, which corresponds with a Rancho Los Amigos Scale level 4 (agitated and confused) and generally resolves prior to resolution of PTA.[54] These agitated behaviors can profoundly affect the patient, caregiver, and treatment team. The diagnosis of posttraumatic agitation is considered a "diagnosis of exclusion" after all medical (infection, metabolic and endocrine abnormalities, pain) and neurologic (e.g., hydrocephalus, intracranial lesion, migraines) causes have been ruled out. The first line of treatment should be nonpharmacological management of environmental factors with the following interventions: (1) reduction in the level of stimulation by limiting the number of visitors, unnecessary sounds, and removing noxious stimuli (e.g., tubes, catheters, restraints); (2) protecting patient from harming self or others by placing them in a padded room, netbed, or vail bed, as well as placing the patient on one-to-one observation; and (3) reducing the patient's cognitive confusion by maintaining consistency with staff and providing brief and effective communication. The next step in treatment is the pharmacological management of agitation. Data provided in a Cochrane Review showed that β-blockers had the best efficacy for treatment of posttraumatic agitation.[55] Numerous drugs have been tried in the management of aggression in TBI, but there has been no firm evidence of their efficacy. Therefore, it is important to choose drugs with few side effects and to closely monitor their impact on the patient.

Posttraumatic Seizures

Posttraumatic seizures can be classified into three categories: immediate PTS (within 24 hours), early PTS (24 hours–7 days), and late PTS (after 7 days).[56,57] Posttraumatic epilepsy (PTE) is defined as two or more unprovoked seizures that occur at least 7 days after a TBI. Posttraumatic epilepsy accounts for 20% of symptomatic epilepsy in the general population and 5% of all epilepsy cases.[58] Approximately 5 to 7% of the 250,000 patients hospitalized annually with TBI experience PTS. Risk factors for early PTS include GCS less than 10, immediate seizure, depressed skull fractures, penetrating head injury, brain contusions, intracranial hemorrhage, PTA more than 30 minutes, chronic alcoholism, and age older than 65.[59–61] Poorly controlled seizures are associated with worsening functional and psychosocial outcome, and impairments with activities of daily living; thus controlling seizure is paramount in long-term recovery.[62] The Brain Trauma Foundation guidelines and the American Academy of Neurology recommend prophylaxis with phenytoin for early PTSs for 7 days for the prevention of late PTSs.[57,61] Also, newer drugs such as levetiracetam have demonstrated efficacy similar to phenytoin for early PTS prophylaxis without the serum monitoring and side-effect profile of phenytoin. Although levetiracetam may be a reasonable alternative choice to phenytoin, caution is warranted because the long-term side effects have not been studied.[63,64]

Neuroendocrine Disorders

Posttraumatic neuroendocrine disorders in TBI patients are often missed or unrecognized by their practitioners, leaving functionally impairing or even life-threatening syndromes unnoticed. The pituitary gland is particularly susceptible to acceleration–deceleration injuries due to the vulnerability of its vascular supply through the infundibulum and firm encasement within the sella turcica.[65] Incidence of hypopituitarism is high in the TBI population with estimates up to 40%.[66] Hypopituitarism is defined as a partial or complete loss of a combination of any of the six hormones secreted from either the anterior or posterior division of the pituitary gland.[65] These hormones have widespread endocrine regulatory purposes, and their dysfunction can lead to a myriad of generalized signs and symptoms that are frequently attributed to expected sequelae of TBI, such as fatigue, cognitive dysfunction, and mood disturbances.[67] A study of neuroendocrine disorders in TBI patients by Agha et al reported 18% incidence of growth hormone (GH) deficiency, 16% with adrenocorticotropic hormone (ACTH) deficiency, 52% hyperprolactinemia, 40% with either diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone (SIADH), as well as a notable reduction in serum thyroid-stimulating hormone (TSH) levels.[68] The most potentially severe syndrome, adrenal insufficiency, can manifest as orthostasis, autonomic dysfunction, nausea, vomiting, and fatigue; it can lead to impairment of the body's stress response. Hypothyroidism can manifest as cold intolerance, weight gain, arthralgias and myalgias, menstrual dysfunction, psychiatric issues, and gastrointestinal (GI) motility problems. Hypotestosteronism results in decreased lean muscle mass. Similarly, GH deficiency can lead to decreased lean body mass, as well as osteoporosis, decreased cardiac function, and reduced cardiovascular endurance. Syndrome of inappropriate antidiuretic hormone and DI can cause hyponatremia; DI may result in profound dehydration. Hyperprolactinemia, which is either due to excess production of prolactin or reduced dopamine, can result in unwanted breast development and erectile dysfunction in men or infertility, menstrual dysfunction, or galactorrhea in women.[65] The recommendations for screening for hypopituitarism in TBI have evolved over the last decade. The consensus guidelines on screening for neuroendocrine disorders following TBI by Ghigo et al suggest that hormonal screening be performed as clinically indicated during the acute hospital stay and again at 3 and 12 months postinjury.[69] They also suggest that those who have a history of moderate-to-severe TBI more than 12 months prior who are being evaluated for the first time should have a screening at the initial visit. However, current recommendations involve screening all moderate-to-severe TBI patients beginning with surveillance for hypoadrenalism with a morning cortisol level within the first 7 days postinjury. At 3 and 6 months postinjury, TBI patients should be screened with a

panel consisting of free T4, TSH, testosterone, luteinizing hormone, and follicle-stimulating hormone levels. Those with abnormalities should be treated with hormone replacement therapy and have levels re-evaluated in 1 year. Growth hormone evaluation requires specialized tests that often require consultation with an endocrinologist. Growth hormone testing should be done 1 year after the injury as abnormalities can be transient.[67] For those who are found to have neuroendocrinopathies post-TBI, hormone replacement therapy has the potential to reduce morbidity and improve overall functional outcome.

Spasticity

Spasticity is a common complication of TBI and is thought to be caused by a loss of central inhibition of the spinal stretch reflex and α motor neuron activity with resultant velocity-dependent resistance to passive stretch accompanied by excessive contraction of the muscles.[70] Some of the risk factors for the development of early spasticity include older age, the severity of brain injury, associated spinal cord injury, hypoxic/ischemic insult, and dysautonomia.[71] Spasticity is particularly problematic in issues of functionality, mobility, pain, skin breakdown, and impaired hygiene. However, there are certain circumstances when increased spasticity can be beneficial, such as providing stability for transfers and to aide in ambulation. First-line management of spasticity includes conservative, nonpharmacological interventions, such as aggressive stretching programs and the use of physical modalities with trained physiotherapists, as well as the use of routine splinting and serial casting. In addition, electrical stimulation of target muscles can be used to fatigue spastic muscles and activate antagonist muscles.[71] Many patients will also require the use of medications for spasticity management (see ►**Table 2**). Reversible causes of increased tone, such as uncontrolled pain or infections, must be addressed prior to initiation or titration of any pharmacotherapy.[70] To avoid the side effects of the oral medications, particularly those that are central nervous system-mediated, focal spasticity may be treated with botulinum toxin or phenol injections.[72] Patients with refractory spasticity can be considered as surgical candidates for interventions, such as posterior rhizotomy or tendon release and muscle-lengthening surgery.[70]

Deep Vein Thrombosis

Several studies indicate that head injury is an independent risk factor for deep vein thrombosis (DVT) in trauma patients.[73] Additional risk factors include male gender, age greater than 55 years, SAH, increased injury severity, and associated lower limb injuries.[74] Contrast venography is the gold standard for the diagnosis of DVT, but its use is limited by cost, invasiveness, potential for complications, and associated pain. Doppler ultrasound, with 89 to 96% sensitivity, 96 to 100% specificity, and more practicality, has been the most frequently used test to evaluate for DVT.[74] To date, no standardization of venous thromboembolism (VTE) prevention has been agreed upon in the moderate-to-severe TBI population due to the ongoing debate regarding bleeding risk associated with the use of chemoprophylaxis. Venous thromboembolism affects ~30 to 54% of moderate and severe TBI patients when pharmacological prophylaxis is not used.[75,76] The majority of research dedicated to this topic has been limited to retrospective and observational studies with small sample sizes that have shown mixed results about the safety regarding the timing of VTE chemoprophylaxis as well as the selection of an appropriate anticoagulation therapy. In their 2007 guideline, the Brain Trauma Foundation merely stated that anticoagulation should be used, but evidence regarding timing is lacking.[59] Currently, there remains no strong evidence to establish clinical practice guidelines with regards to the use of chemoprophylaxis in TBI patients with intracranial hemorrhage.[77] Many practitioners use nonpharmacological means of mechanical prophylaxis with compression stockings, sequential compression devices, or venous foot pumps.[74] A method of pulmonary embolism (PE) prevention that has gained greater use in the acute care setting is the insertion of temporary inferior vena cava filters in the patient with known lower limb DVT, but who also has contraindications to anticoagulation medication.[74]

A retrospective cohort study with intracranial hemorrhage by Koehler et al claimed that the administration of low-molecular-weight heparin (LMWH) within the first 72 hours post brain injury reduces the risk of VTE and PE postinjury with no evidence that early VTE prophylaxis increases the rate of intracranial hemorrhage progression in hemodynamically stable patients.[78] But the incidence of VTE in this study was likely underestimated given that they relied solely on clinical manifestations rather than performing scheduled screening. Another retrospective study by Minshall et al reviewed the use of enoxaparin and unfractionated heparin for VTE prevention post-TBI and found enoxaparin had significantly better protective effects against VTE and lower intracranial bleeding complications compared with unfractionated heparin.[79] However, patients in the heparin group had many more severe brain injuries, thereby biasing the results. In his literature review on the body of evidence regarding VTE prophylaxis, Phelan makes the astute observation that up to this point inclusion criteria for these studies consist of the presence and absence of intracranial hemorrhage. This would suggest that the risks for spontaneous progression and the times necessary for stabilization of hemorrhage patterns are the same across all sizes and scopes of injury, thereby leading to a single standardization of VTE prophylaxis protocols for all types of TBI patterns. This is not what is seen in clinical practice, and the propensity for progression of an intracranial hemorrhage has been shown to be related to the severity of injury.[76] Needless to say, much more research is needed to progress toward a standardization of VTE prophylaxis in TBI patients.

Sleep

Although the exact prevalence of posttraumatic sleep disturbances after TBI are difficult to decipher, it is estimated to

Table 2 Medications used for the treatment of spasticity[70,71]

Medication	Mechanism of action	Side effects
Baclofen	Inhibits spinal reflex and decreases α motor neuron activity by binding GABA B receptor at the spinal cord level	Muscle weakness, sedation, fatigue, dizziness, nausea, elevated LFTs; abrupt cessation associated with withdrawal syndrome (seizures, hallucinations)
Diazepam	Binds GABA A receptor	Sedation, cognitive impairments, potential for dependence; abrupt cessation associated with withdrawal (seizures)
Tizanidine	Alpha-2-adrenergic agonist, which inhibits the release of excitatory neurotransmitters by spinal interneurons	Xerostomia, drowsiness, dizziness, visual hallucinations (rare), elevated LFTs, hypotension
Clonidine	Centrally acting α-2-adrenergic agonist, which is believed to decrease sympathetic outflow	Bradycardia, hypotension, xerostomia, drowsiness, constipation, dizziness, depression
Dantrolene	Inhibits skeletal muscle contraction directly by inhibiting calcium release from muscle sarcoplasmic reticulum	Weakness, drowsiness, diarrhea, malaise, hepatotoxicity (severe)
Gabapentin	Exact MOA is unclear, but structurally similar to GABA	Sedation, edema
Botulinum toxin (intramuscular)	Blocks presynaptic release of acetylcholine, inhibiting neuromuscular coupling and muscle contraction	Complications associated with procedure (pain, infection, bleeding), excessive weakness, dysphagia
Intrathecal baclofen	Same as oral regimen, but intrathecal delivery allows for higher concentration at a lower dose compared with oral administration, thereby minimizing neurologic adverse effects	Drowsiness, headaches, nausea, hypotension, coma (rare), mechanical complications (dislodged, blocked, or kinked catheter or pump failure), infection

Abbreviations: LFTs, liver function tests; MOA, mechanism of action.

occur in roughly 30 to 70% of head-injured patients.[80] Reported sleep complaints following TBI include hypersomnia, excessive daytime somnolence (EDS), insomnia, and altered sleep–wake cycles that all may manifest as a mood disorder. Excessive daytime somnolence can also be associated with sleep apnea and narcolepsy.[81] There are multiple studies postulating that the type of sleep disturbance resulting from TBI can depend more on the location of injury within the brain and less on its severity. Hypersomnia can be seen when areas involving wakefulness are affected, such as the reticular formation and posterior hypothalamus.[80] However, this potential association of sleep disturbances with specific anatomical lesions requires further inquiry. Other studies have concluded that sleep disturbances in this patient population are multifactorial, including the presence of an overlying diagnosis of depression, increased slow-wave sleep, disruption of circadian regulation of melatonin, and reduced rapid eye movement.[81] Objective testing with polysomnography and multiple sleep latency testing can be useful in the workup of these patients.[80]

Prior to initiating pharmacotherapy, patients must be educated on how to manage daytime fatigue and initiation of good sleep hygiene techniques including avoiding daytime naps, adhering to a regular bedtime schedule, and avoiding time spent in bed awake.[81] There is some data that suggest cognitive–behavioral therapy and acupuncture can improve the quality of nocturnal sleep.[80] Comorbid conditions that could be disrupting sleep, such as restless leg syndrome, obstructive sleep apnea, depression, or pain complaints must be adequately managed. Only after these issues have been addressed should pharmacological interventions be employed. Benzodiazepines and benzodiazepine-like medications, such as zolpidem, are poor choices for long-term insomnia management given their side-effect profile, which include inhibition of neurorecovery and addiction-like properties. Neurostimulants, such as methylphenidate or Modafinil, may be used for daytime somnolence or narcolepsy and could be beneficial to promote alertness during the day, which may in turn help promote sleep at night. Modafinil has not been shown to be effective in treating fatigue, but has shown to be effective in treating or excessive daytime sleepiness post-TBI.[82] Melatonin has been reported to improve sleep latency in chronic insomnia, but only one randomized control trial has investigated its use to treat sleep disturbances in patients with TBI. It failed to show significant improvement in sleep parameters, but was limited by sample size.[81]

Psychological Factors

Mood problems, anxiety, apathy, personality change, emotional lability, aggression, substance use, and psychosis (less commonly) have all been reported following moderate and

severe TBI.[83] Discerning whether psychological symptoms are directly due to neurologic insult or patients' reaction to injury is often difficult. Clinicians must also consider the impact of other TBI-related deficits that can negatively affect mood, most notably sexual dysfunction, sleep disturbance, pain, fatigue, cognitive limitations (including anosognosia or anosodiaphoria), and poor coping strategies.

Among the possible psychological consequences of TBI, depression is the most recognized by clinicians and researchers alike.[84,85] Methodological challenges and variability in assessing mood symptoms has led to a range of prevalence estimates for depression following TBI. A recent meta-analysis examined clinically diagnosed and self-reported depression and found that ~30% of severe TBI patients met clinical criteria for depression or dysthymia (in contrast to 16% of mild TBI patients), and 39% surpassed cutoff scores for depression on self-report measures (in contrast to 64% of mild TBI patients).[86] Risk factors for postinjury depression include younger age, being a white female, lower education, preinjury mood or medical problems, lifetime alcohol use, preinjury work instability, inadequate social support, and poor physical functioning.[87–89] Unlike most problems following TBI, which either improve or remain stable in the chronic stages, depression has the potential to begin long after the injury or worsen over time, even over the course of decades.[90] Nonetheless, the rate of depressive symptoms appears greatest within 1 month of injury, and the incidence of new-onset depression is 50% after controlling for mood at the time of injury.[87] A growing body of literature has shown that psychological interventions for depression after moderate-to-severe TBI have demonstrated medium effect sizes overall.[91,92] It should be noted that cognitive–behavioral treatments (CBT) are the most frequently utilized psychological interventions; however, a blanket application of CBT would be inappropriate because psychological services must be tailored to each patient based on their level of awareness, cognitive functioning, behavioral control, and personal preferences.[25] First-line psychopharmacological intervention for depression typically involves the use of selective serotonin reuptake inhibitors, with sertraline and citalopram having the strongest evidence base.[93–95] Sertraline also likely has the added benefit of stimulating cognitive functioning.[96] Ultimately, the combination of both pharmacotherapy and psychological services appear to yield the best outcomes in this population.[25]

Cognitive Rehabilitation

Changes in cognitive, behavioral, emotional, and personality functioning are often the most debilitating sequelae of TBI, particularly with regard to the recovery of social and occupational functioning.[97] Deficits are variable across patients and are dependent on many factors beyond those that are typically used to grade injury severity (i.e., GCS, LOC, PTA). The heterogeneous presentation of symptoms is affected by the characteristics of the primary injury (e.g., contact injury or acceleration–deceleration forces vs. penetrating), secondary injuries, acute interventions, and premorbid attributes of the individual (e.g., intellectual functioning, cerebral lateralization, substance use, history of head injuries, age).[98] Although the pattern of behavioral and cognitive deficits following TBI are individualized, research in large samples indicates that deficits in attention, processing speed, memory, and executive functioning are common due to the susceptibility of the frontal and temporal poles to damage and the prevalence of traumatic axonal injury. The etiology, severity, and specific location of lesions in these regions also determine the type of cognitive deficits that are observed. For instance, prefrontal damage circumscribed to the ventromedial aspects of the orbitofrontal cortex can result in executive dysfunction characterized by an inability to make advantageous decisions or adhere to social conventions.[99] However, if frontal lobe lesions also involve the dorsolateral prefrontal cortex, then working memory and attentional control may be impaired. If dorsomedial prefrontal damage occurs, then apathy and an inability to initiate behavior can develop.

Given the heterogeneity of cognitive dysfunction and the myriad of factors that affect its manifestation, formal neuropsychological evaluation is often useful as the first step in the cognitive rehabilitation process. Neuropsychological evaluation aims to extend neuroimaging and the neurologic exam by objectively quantifying the extent to which brain damage affects cognition and behavior. Neuropsychological assessment also guides many rehabilitative therapies by attributing deficits to their appropriate causes to ensure that impairments are properly targeted for treatment. For example, patients may present with what appears to be a memory problem, but it may be that deficits in complex divided attention, vigilance, cognitive processing speed, or executive functioning are causing "upstream" interference with memory that mimics forgetfulness. Regarding behavioral changes, neuropsychological evaluation can help determine if a patient's apathy is due to a cortical lesion or if the apathy is due to a mood disorder (e.g., depression) that can improve with psychological services. In addition to guiding rehabilitation interventions, neuropsychological testing can also identify cognitive barriers that interfere with other rehabilitation efforts. For example, physical therapists can be made aware of subtle deficits in perseveration or behavioral disinhibition that pose safety risks to patients as they gain mobility or attempt transfers.

After neuropsychological deficits are identified, then relevant cognitive rehabilitation and psychological services are initiated. Cognitive rehabilitation strategies are implemented based on the expertise of the clinician and they are most often conducted by neuropsychologists, rehabilitation psychologists, speech pathologists, and/or occupational therapists. There are many ways to conceptualize cognitive rehabilitation; most tend to fall on a continuum ranging from holistic to deficit-focused approaches.[100] Holistic approaches emphasize the importance of complimentary activities that include establishing a therapeutic milieu (e.g., a supportive environment, rapport), cognitive retraining, psychological services (i.e., individual or group therapy), ongoing involvement and education of family members, and "protected work trials" where patients can engage in relevant real-world tasks

without failure resulting in adverse consequences.[101] Deficit-focused approaches focus on targeted interventions designed to treat specific cognitive impairments. In our experience, many rehabilitation professionals fall somewhere in the middle of the holistic–deficit-focused continuum and tend to recognize the interrelatedness of cognition, mood, and social functioning; the importance of social support; and the need to draw on multiple disciplines to maximize patient outcomes.[102]

Cognitive rehabilitation interventions themselves can be roughly categorized as restorative, compensatory, or metacognitive although the distinctions between these categories are somewhat blurred in reality. Restorative strategies are aimed at directly reducing specific cognitive deficits through drills and exercises and tend to be used in the acute stage of recovery if they are utilized.[100,103] It should be noted that the effectiveness of restorative therapies is controversial in the research with only a few interventions showing mildly demonstrable effects.[104] Examples of restorative therapies that may be worthwhile include direct attention training that aims to improve attentional capacity through the administration of increasingly difficult attention tasks and visuospatial training for patients with neglect syndromes.[104] In contrast to restorative interventions, compensatory strategies are more heavily utilized after maximum cognitive recovery has occurred (i.e., 1–2 years postinjury). As the name suggests, these strategies compensate for persisting deficits by teaching patients to rely on remaining cognitive abilities or external aids to reduce the functional impact of impairments. For example, patients with deficits in explicit memory can be encouraged to depend on their implicit/procedural memory through the proper use of a routine or through the use of assistive technology as an external aid (i.e., smartphones). Metacognitive strategies are those that train patients to "think about their thinking" regarding specific tasks (e.g., overarching memory strategies to increase retention) or general techniques that can be applied to all cognitive processes. General metacognitive techniques include self-monitoring, self-instruction, goal attainment and management training, time-pressure management, and problem-solving processes.[103] Regardless of the clinician's emphasis on restorative, compensatory, or metacognitive interventions, research has supported (to varying degrees) the use of cognitive rehabilitation intervention for improving general cognitive functioning following TBI.[104–106]

Prognosis and Common Outcomes Measures

Specific cognitive, behavioral, and medical outcomes following TBI are highly individualized due to the noted variability in injury and patient characteristics. As a result, the majority of TBI outcome research has focused on global functional outcomes. For instance, the most widely used outcome measurement tool in the literature is the Glasgow Outcome Scale (GOS), which rates recovery according to five broad classifications: dead, persistent vegetative state, severe disability (i.e., cannot live alone for more than a day), moderate disability (i.e., able to work in a supportive environment and function independently at home), and good recovery (i.e., able to resume normal occupational duties and social functioning despite minor persisting impairments).[107] In a landmark study, Steyerberg and colleagues developed a prediction algorithm for GOS at 6 months using data from over 8,500 patients with moderate or severe TBI from the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) project.[108,109] They then used a large cohort from the Medical Research Council Corticosteroid Randomisation after Significant Head Injury (MRC CRASH) randomized clinical trial for external validation.[110] Clinical variables obtained upon admission were analyzed and the following predictors had the greatest prognostic value: age, GCS motor score, pupillary reactivity, hypoxia, hypotension, CT results based on Marshall CT classification, traumatic SAH, epidural hematoma, glucose (mmol/L), and hemoglobin (g/dL).[111] The study authors have created an online prognostic calculator utilizing the above predictor variables to aid clinicians in determining the probability of 6-month mortality or unfavorable outcome (i.e., GOS indicating severe disability or vegetative state). The prognostic calculator is available on the IMPACT Web site (http://www.tbi-impact.org/?p=impact/calc). The prediction of cognitive recovery following moderate and severe TBI is more difficult than predicting global functional outcome given the heterogeneous presentation of neuropsychological deficits following head injury. Broadly speaking, cognitive recovery tends to occur most rapidly within the first year after injury, but then plateaus at 2 years postinjury.[83,112] A linear relationship exists between TBI severity and persisting cognitive deficits. Dikmen and colleagues demonstrated this well by comparing a sample of TBI patients to general trauma patients on several neuropsychological measures at 1 year follow-up. Results indicated that patients who were able to follow commands within 24 hours did not differ from non-TBI trauma patients at 1 year. In contrast, patients who did not follow commands for a day or more exhibited persisting cognitive deficits 1 year later. The cognitive domains most susceptible to impairments were nonverbal abilities (i.e., fluid intelligence), delayed verbal memory, cognitive processing speed, and bilateral fine psychomotor speed. Patients who took more than 14 days to respond to commands exhibited chronic deficits across all assessed cognitive domains, with worsening TBI severity resulting in proportionately more profound persisting deficits. A follow-up study was consistent with these findings and demonstrated that chronic declines in cognitive competency was one of the most persistent patient-reported changes following TBI, with 60% reporting they have not returned to their cognitive baseline 3 to 5 years postinjury.[84] In addition to the GOS, other outcome measures are often used throughout rehabilitation to broadly assess neurobehavioral recovery, functional outcomes, level of cognitive function, and to predict outcomes and effectiveness of treatment interventions.[113] There are numerous measures that have been used; the most commonly used outcome assessments are discussed below.

The Functional Independence Measure (FIM) is a widely used measure on inpatient rehabilitation units. It is an 18-item measure with a 7-point ordinal scale that ranges from

total assistance to complete independence. The FIM broadly assesses domains of self-care, mobility, and cognition; items are summed into a gross cognitive subscale (5–35), motor subscale (13–91), and overall FIM total score (18–126). The FIM aids in tracking improvements in functional independence during treatment, predicting LOS, and determining level of supervision on discharge.[32]

The Rancho Levels of Cognitive Functioning Scale (Rancho Scale) is an 8-level ordinal scale that assesses level of recovery after brain injury based on interaction with the environment.[54] The Rancho Scale provides clinicians with a gross assessment of recovery that can be used to establish targeted outcomes and build a treatment program.

The Galveston Orientation and Amnesia Test (GOAT) and Orientation Log (O-Log) are two validated measures to assess the length of posttraumatic amnesia. The GOAT is a 10-item measure that assesses orientation and memory for events prior to and after the event. Two consecutive administrations of the GOAT with a score $\geq$ 76 are consistent with emergence from PTA.[114] The O-log is a brief measure used to assess orientation, which includes questions related to place, time, and situation. The O-Log requires that a person obtains $\geq$ 25 points on two consecutive occasions over 72 hours to clear PTA. The O-Log offers better prediction of rehabilitation outcomes when compared with the GOAT.[94,115]

The Disability Rating Scale (DRS) was developed to track changes through the spectrum of brain injury recovery from coma to the community.[116] Scores range from 0 (no disability) to 29 (extreme vegetative state). The DRS evaluates eight areas of functioning in four categories: (1) consciousness, (2) cognitive ability for self-care, (3) dependence on others, and (4) employability. Of note, the DRS has been shown to be more sensitive than the frequently used Glasgow Outcome Scale-Extended.[117]

Conclusion

Traumatic brain injury is a major cause of morbidity and disability and is considered a major public health concern. Traumatic brain injury is caused by an external force leading to an alteration in brain function or other evidence of brain pathology.

The goal of acute management is focused on medical stabilization and prevention of secondary injury through surgical and nonsurgical interventions. The severity of a TBI can range from mild to severe and is classified based on GCS, LOC, duration of PTA, and structural neuroimaging. Moderate-to-severe TBI sequelae can lead to a myriad of complex medical, psychological, cognitive, and social impairments requiring a true interdisciplinary team to optimize functional outcomes, prevent disability, and maximize independence.

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