

HOSPITAL PHYSICIAN®

NEUROLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Neurology Board Review Manual* is a peer-reviewed study guide for residents and practicing physicians preparing for board examinations in neurology. Each manual reviews a topic essential to the current practice of neurology.

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Traumatic Brain Injury: Rehabilitation Neurology

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Traumatic Brain Injury: Rehabilitation Neurology

Anthony J.W. Chen, MD

INTRODUCTION

Traumatic brain injury (TBI) affects an estimated 1.4 million individuals in the United States each year.¹ Although the injuries are acute, functional deficits that result from TBI may produce tremendous chronic physical, emotional, and financial burdens on individuals, families, and health care systems. TBI is a leading cause of long-term disability in the United States.^{2,3} Studies suggest that up to 2% of the US population lives with disabilities resulting from brain injury.^{1,4,5} Individuals with TBI are at risk for being unable to live independently. Surveillance for TBI across 14 states showed that approximately one third of patients continue to require assistance with daily activities 1 year after injury.⁶ For patients hospitalized for TBI, cognitive status is a major factor in determining whether individuals are discharged to institutions.⁷


Care for patients with TBI is a major part of neurology practice. TBI is one of the most common neurologic diagnoses in the United States.⁸ The role of the neurologist varies in different practice settings, ranging from acute emergency services to care in rehabilitation or community outpatient settings. TBI is marked not only by an acute injury superimposed on a prior baseline neurologic state, but also by dynamic post-injury factors that may encourage or hamper functional recovery over the long term. An important goal of neurologic TBI care is to identify and manage these factors to maximize functional outcome.

Neurologic deficits caused by TBI are not unique to trauma per se, but certain patterns of dysfunction are more common with TBI than other causes of injury. While these patterns are partially explained by traditional neurologic localization of focal cerebral lesions, the localization approach has left many TBI sequelae poorly explained. As illustrated by the cases presented in this manual, sources of dysfunction in the course of TBI may be complex and varied, involving not only the pathophysiology of direct impact injury, including shearing forces, but also subsequent medi-

cal complications, changes in physical, cognitive, and social status, reactive and layered emotional responses to a new personal status, and medications and other medical management decisions. It is important for the neurologist to understand the multifaceted nature of TBI and participate in the multidisciplinary approach to evaluation and management that many patients with TBI require. This review is focused primarily on rehabilitation-related neurologic care and closed-head injury, with consideration of aspects of care in the post-acute to chronic stages of recovery.

SEVERE INJURY: INJURY RATINGS, NEUROLOGIC LOCALIZATION, AND PROGNOSIS

CASE PRESENTATION I

 Responding to a 911 call, an emergency medicine technician (EMT) finds a 25-year-old man on the street outside a building where a party had spilled over to a third floor balcony. Witnesses say that the patient stepped out for fresh air and tripped when additional crowds pushed onto the balcony. On initial assessment, the EMT documents no eye opening, incomprehensible vocalizations, and an extensor motor response to pain. The patient remains unconscious for 4 days. He then begins opening his eyes and responding to his environment, including following commands, but he remains disoriented and confused until 2 weeks after this injury. A neurologist is asked to formulate a prognosis for this patient's eventual functional outcome to help prepare the family regarding expectations for his recovery.

- **What information derived from the acute injury period may help with formulating a prognosis for recovery?**

Estimating prognosis based on acute injury factors is an imprecise but reasonable start. The severity of initial injury (mild, moderate, or severe) correlates with long-term functional outcomes at a broad level. Glasgow Coma

Table 1. Criteria for Initial Severity Ratings in Traumatic Brain Injury

Severity Rating	Duration of Loss of Consciousness	Glasgow Coma Scale Score	Posttraumatic Confusion Duration
Severe	≥ 24 hr	< 8	≥ 7 days
Moderate	> 30 min < 24 hr	8–12	> 24 hr < 7 days
Mild	0–30 min	13–15	≤ 24 hr

Scale score (GCS), duration of posttraumatic confusion (or amnesia [PTA]), duration of coma, and age have been found to correlate with outcomes.⁹ Neuroimaging findings may also provide important information, but the relationships may be more complex. In particular, the presence of subarachnoid hemorrhage, cisternal effacement, significant midline shift, and epidural hematoma or subdural hematoma on acute computed tomography (CT) scan are associated with worse outcomes.⁹

• **What is the initial severity of this patient’s TBI?**

Initial severity ratings are commonly classified based on duration of loss of consciousness (LOC), the initial GCS score, and duration of PTA (Table 1). The GCS score is used acutely to define the depth and duration of coma and is calculated based on 3 parameters: eye opening, best verbal response, and best motor response (Table 2). Based on the available information, this patient had an initial GCS score of 5: 1 for lack of eye opening to any stimuli, 2 for incomprehensible speech, and 2 for extensor response to pain. PTA is marked by a period during which the individual is disoriented and encoding new information poorly. The duration of PTA is best determined prospectively during acute evaluation. Therefore, the evaluation performed later in the recovery course may have to rely on records from initial evaluators. The information that is useful in this early evaluation is well operationalized in the Galveston Orientation and Amnesia Test (GOAT), a simple and reliable test for assessing PTA (Table 3). The test questions help determine loss of memory for events prior to the injury and time until memory of events following injury. The end of the period of PTA is marked by 2 consecutive days with a GOAT score greater than 75. The case patient’s PTA resolved after 14 days. At that time, he was oriented and able to respond sparsely but appropriately to questions. Given his duration of LOC, GCS score, and duration of PTA, this patient experienced a severe TBI.

Table 2. The Glasgow Coma Scale

I. Motor response	
6	Obeys commands fully
5	Localizes to noxious stimuli
4	Withdraws from noxious stimuli
3	Abnormal flexion (ie, decorticate posturing)
2	Extensor response (ie, decerebrate posturing)
1	No response
II. Verbal response	
5	Alert and oriented
4	Confused, yet coherent, speech
3	Inappropriate words and jumbled phrases consisting of words
2	Incomprehensible sounds
1	No sounds
III. Eye opening	
4	Spontaneous eye opening
3	Eyes open to speech
2	Eyes open to pain
1	No eye opening

• **Based on initial findings, what is this patient’s long-term prognosis?**

Although this is a commonly asked question, prognostic statements generally must be limited to stating that initial GCS and early injury characteristics increase or decrease the likelihood of good recovery in a general way, and few specific individual predictions can be made. It is now well accepted that acute injury severity, GCS score, PTA, and coma duration do correlate with functional outcomes; however, it is important to recognize that the range of recovery is extremely broad, and early injury variables are not predictive with great accuracy in any individual case.^{10,11} The latter point is underscored by the clinical experience that patients with equivalent lengths of LOC, coma, or PTA may have very different outcomes, where one patient may remain in a persistent vegetative state 1 year later, while another patient may walk into an outpatient clinic after 1 year, verbally describing his current efforts to reintegrate into the community. Furthermore, studies have been limited by the lack of sensitivity of functional rating scales at the higher levels of functioning. For example, the commonly used Glasgow Outcome Scale only has 5 divisions (Dead, Vegetative State, Severe Disability, Moderate Disability, and Good Recovery). Good recovery does not necessarily mean that the individual has no residual

Table 3. Galveston Orientation and Amnesia Scale

	Error Points
What is your name?	2
When were you born?	4
Where do you live?	4
Where are you now?	
City?	5
Hospital? (unnecessary to state name of hospital)	5
On what date were you admitted to this hospital?	5
How did you get here?	5
What is the first event you can remember after the injury?	5
Can you describe in detail (eg, date, time, companions) the first event you can recall after the injury?	5
Can you describe the last event you recall before the accident?	5
Can you describe in detail (eg, date, time, companions) the first event you can recall before the injury?	5
What time is it now?	1 for each half hour removed from correct time to maximum of 5
What day of the week is it?	1 for each day removed from correct one
What day of the month is it?	1 for each day removed from correct date to maximum of 5
What is the month?	5 for each month removed from correct one to a maximum of 15
What is the year?	10 for each year removed from correct one to maximum of 30
Total error points	
Total score (100 – total error points)	


Adapted with permission from Levin HS, O'Donnell VM, Grossman RG. The Galveston orientation and amnesia test: a practical scale to assess cognition after head injury. *J Nerv Ment Dis* 1979;167:675–84.

deficits, and the most common residual problems are in neurobehavioral domains of functioning that are not specifically incorporated into this rating.

Based on systematic review of available studies documenting early injury features and functional outcomes, the following 2 threshold situations appear to be supported.⁹ *Severe disability* is unlikely when time to follow commands is less than 2 weeks and duration of PTA is less than 2 months. On the other hand, *good recovery* is unlikely when time to follow commands is longer than

1 month, duration of PTA is greater than 3 months, and age is greater than 65 years. Any prognostic statement needs to be tempered with the caveat that although data may be helpful at a broad population level, prognosis at the individual level cannot be determined with certainty.

CASE 1 CONTINUED

 During the patient's hospital course, the consulting physicians are concerned that the patient may be at risk for seizures. Following consultation with a neurologist, they start the patient on phenytoin for seizure prophylaxis in the hospital setting. He has no seizures during his hospitalization. The patient is transferred to an acute rehabilitation facility 1 month later.

- **The consulting physicians ask whether prophylactic AED use will help prevent posttraumatic epilepsy. Should this patient continue to receive AEDs?**

PHARMACOTHERAPY, POSTTRAUMATIC SEIZURES, AND EPILEPSY


There is strong evidence that AEDs are effective in preventing seizures in the early injury recovery course. Phenytoin and carbamazepine are most commonly used, and randomized controlled trials provide evidence that they reduce the rate of early seizures.¹² It is reasonable to initiate AED therapy early after TBI, ensuring that levels are kept within therapeutic range. However, available clinical studies testing phenytoin, carbamazepine, and valproate do not support a significant benefit of AED use in preventing late seizures (those occurring after 7 days). Routine use of AEDs for the purpose of decreasing the risk of late posttraumatic seizures is not recommended.^{13,14} Furthermore, the continued use of AED therapy for prophylaxis in the absence of epilepsy is not recommended. Even in the context of documented posttraumatic seizures, the overall decision to continue AED treatment must take into account other factors, such as the level of potential detrimental effects of seizures to the patient's medical status, care, or lifestyle (eg, driving), as well as potential adverse effects of medication that could include cognitive and behavioral dysfunction, ataxia, rashes, and other effects.

- **When the patient is admitted to the rehabilitation unit, his medications include phenytoin for seizure prophylaxis, haloperidol and benzodiazepines for behavioral dyscontrol and aggression, baclofen for spasticity, and sertraline for depression. Which of these medications would be particularly concerning for possibly impeding his functional recovery?**

ADVERSE EFFECTS OF PHARMACOTHERAPY IN RECOVERY AND REHABILITATION

Patients with TBI may have medications added to their therapeutic regimen to deal with issues during the many phases from acute injury to chronic recovery. Phenytoin has been shown to impair cognitive functioning in patients with severe TBI.^{15,16} Carbamazepine may also have cognitive side effects.¹⁷ Among older antiepileptic agents, valproate may be preferable. Benzodiazepines and baclofen are γ -aminobutyric acid (GABA) agonists, and these may reduce the rate of recovery from TBI.¹⁸ The use of these medications should be minimized during recovery from TBI. In certain circumstances, spasticity may be treated by more localized means (eg, intrathecal baclofen or targeted botulinum toxin). Dopamine antagonists, such as haloperidol, have been shown to impede learning and recovery.^{19–23} These agents are commonly used for managing behavioral dyscontrol, but they should be used sparingly and continual use should be avoided as much as possible. It is important to repeatedly review the rationale and necessity of each medication at each clinical juncture, with a concern for potential adverse effects on recovery. It is often necessary to remove medications before further determining sources of dysfunction. Indeed, cessation of medication is often as valuable as starting any medications in the rehabilitation course.

CASE 1 CONTINUED

 At a follow-up neurology consultation 12 weeks after the initial injury, the patient is able to speak but with dysarthria, requires assistance to feed himself, and is able to ambulate but requires assistance. He is able to express his needs and opinions. The patient's family is continuing to struggle to understand their loved one's situation. Although the patient continues to improve in terms of gait, speech, and other basic functions, he continues to have difficulties with behavioral outbursts, anger, and socially inappropriate behavior. The family asks whether it is possible to provide more information regarding these specific problems.

- **Can imaging studies help to explain what areas of this patient's brain were injured and further inform his course of recovery?**


LOCALIZATION

The most common sites of detectable injury after closed head injury are determined by vulnerability to resistive forces by the skull. The frontal lobes in the

orbitofrontal regions in particular may be injured by the rough surface of the cribriform plate. Inferolateral frontal regions may be contused by the sphenoid bone. Anterior and mesial temporal lobes are also highly vulnerable due to the enclosure by the skull. Coup injuries occur adjacent to the location of external trauma, while contrecoup injuries are typically caused by inertial and impact forces on the opposite side of the brain with rapid changes in direction. Location of injury may vary greatly depending on the specific mechanics at the time of injury.

The previously discussed prognostic considerations were limited to broad ratings of functional outcomes. More specific statements may be possible in individual cases based on more detailed evaluation of lesions and neurologic status. For example, knowing that a patient has suffered bilateral orbitofrontal and mesial temporal injury with severe encephalomalacia in those regions suggests that the patient has an increased likelihood of having chronic difficulty with social and emotional regulation. However, the absence of visible lesions does not rule out structural or functional abnormalities.

CASE 1 CONTINUED

 After reviewing early CT scans showing orbitofrontal and temporal contusions, the neurologist orders magnetic resonance imaging (MRI) to gather additional information after resolution of initial swelling and hemorrhage (**Figure 1**). In addition to frontal contusions, the images show enlarged ventricles, widened sulci, and T2 hyperintensities in white matter. The family had previously understood that the patient had "frontal brain injury."

- **How can these newly detected features consistent with generalized atrophy and widespread injury be explained?**

These findings highlight an important feature of neural injury following trauma: axonal injury. Axonal injury may occur due to stretching or shearing forces that often occur with severe TBI. The phenomenon is commonly called diffuse axonal injury (DAI) to highlight the spatially distributed nature of injury, where the diffuse nature is often only presumed given poor visualization of the actual process. Axonal injury may be apparent as T2 hyperintense white matter lesions, although clinical imaging is not sensitive to such injury and this finding is not specific to traumatic DAI (eg, similar findings could occur with small vessel ischemia). DAI does appear to generally worsen the prognosis for recovery. Although difficult to characterize with current imaging

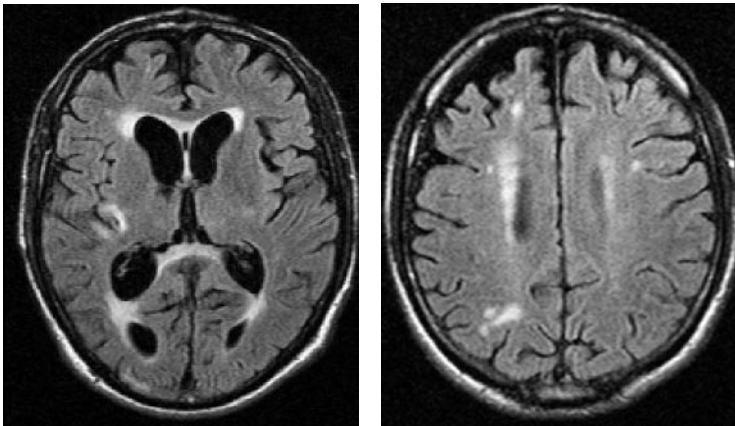


Figure 1. Fluid-attenuated inversion recovery (FLAIR) images from the magnetic resonance imaging assessment of case patient 1, showing enlarged ventricles, widened sulci, and T2 hyperintensities in white matter.

technologies, it is becoming increasingly clear that not all axons are equivalently injured and that localization could be related to specific domains of functioning.^{24,25} Thus, the phenomenon might more accurately be called multifocal axonal injury. Other important sources of diffuse neuronal injury may include hypoxia and ischemia.

Available techniques for increasing the chances of detecting evidence of shear injury include MRI with gradient-echo imaging. Iron deposits from prior hemorrhages, including microhemorrhages, create changes in magnetic susceptibility that are visible as dark areas on gradient echo. Evidence of microhemorrhages is generally interpreted to suggest shearing forces great enough to cause vascular damage and by inference may reflect axonal injury as well. Higher magnetic resonance field strengths and susceptibility-weighted imaging may increase the sensitivity for detection of past microhemorrhages. However, the location of microhemorrhages does not appear to have strong value in localization of brain dysfunction.²⁶ Diffusion tensor imaging may provide measurements of white matter integrity, and functional, pharmacologic, and chemical imaging methods may provide additional information; however, further research is required before these modalities can be applied clinically.^{24,25} An important general conclusion is that the injury in TBI is likely to be more extensive than what is visible on acute clinical imaging.

CASE 1 CONCLUSION

The patient progresses in the rehabilitation facility and is able to return home with family. He is able to perform basic activities of daily living but requires significant supervision due to impulsiveness, poor decision making, and difficulties with social interactions.

FRONTAL INJURY AND EXECUTIVE DYSFUNCTION

CASE PRESENTATION 2

A 45-year-old man who works as a bank executive is transferred to a rehabilitation unit 1 month after being involved in an accident in which he was struck by a bus while turning a street corner on his bicycle. He was wearing a helmet but was thrown off the bicycle and his head struck the ground. He was poorly responsive, confused, and did not open his eyes except to noxious stimuli, even while being transported to the trauma center. Paramedics recorded a GCS score of 10. He became agitated and then more somnolent by the next day. A CT scan performed 1 day after the injury showed left frontal contusion and hematoma with edema (**Figure 2**). Anesthesia was administered and surgical decompression was performed. The patient remained confused and agitated for 7 days.

• What is the severity rating of this patient's injury?

This patient's injury could be rated as a moderate severity TBI based on the GCS score. The period of PTA is confounded by intervening hemorrhage, swelling, surgery, and anesthesia. Note that the traditional severity rating is based solely on initial clinical findings and does not take into account the imaging findings nor subsequent course. Specific lesions resulting in specific neurologic deficits are not characterized by the severity rating. This is a significant limitation of traditional severity ratings, especially if one hopes to use ratings to understand subsequent recovery.

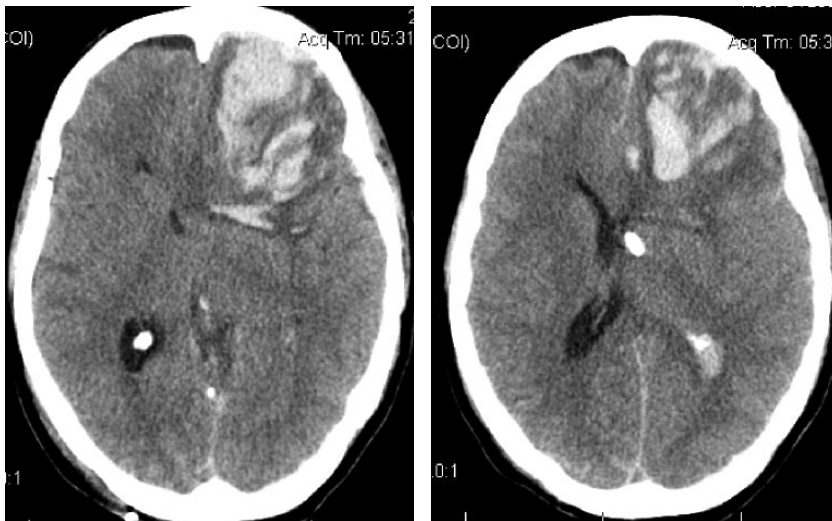


Figure 2. Computed tomography scans obtained 1 day after accident in case patient 2 showing left frontal contusion and hematoma with edema.

CASE 2 CONTINUED

On examining the patient, the neurologist finds that although he is fully oriented, he continues to seem disorganized and highly distractible. When faced with ambiguous instructions or situations requiring choices, he has difficulty proceeding. Prior to the injury, the patient worked to support his family, including 2 children, and his family is very concerned about prognosis, in particular regarding his ability to return to a high-level management position. Based on imaging and exam findings, the neurologist tells the family that the patient may have difficulties associated with frontal lobe damage and refers the patient for neuropsychological evaluation. The neuropsychologist reports that the patient's history and testing are consistent with dysfunction in attention and executive control functioning.

- **What is executive control dysfunction and what are its functional impacts?**

Although it is commonly understood that TBI can result in almost any neurologic deficit, the most common and persistent deficits tend to be in cognitive functions. The abilities of paying attention, holding information in mind, organizing, and developing efficient strategies for completing activities seem to be particularly vulnerable. These functions are often summarized as aspects of executive control or cognitive control, terms that encompass a collection of processes that contribute to goal-directed behavior, including selective attention, working memory, task-switching, sequencing, organization, prioritization, problem-solving, and planning.^{27,28} Deficits in these functions may be related to damage to prefrontal systems, which include not only prefrontal

cortex but extensive interconnections with subcortical and posterior cortical structures. Deficits may also be related to damage to neuromodulatory pathways from the base of the brain to cortex.

Deficits in executive control processes may directly contribute to poor outcomes as well as impede rehabilitation of dysfunction in other neurologic domains.^{29–33} The effects of executive control dysfunction reach far beyond the confines of cognitive dysfunction. At the broadest level, poor executive control leads to disorganized behavior that affects numerous aspects of personal functioning. Executive control functions are crucial for the pursuit of educational and occupational goals^{34–37} with TBI resulting in an increased rate of job turnover and reduced job status.³⁷ Remediation of these functions may be valuable for influencing learning and recovery in other neurologic domains. For example, improved goal-directed functioning may enhance an individual's ability to actively participate in rehabilitation of motor functions, allowing an individual to hold learning goals in mind, selectively attend to learning activities, and solve problems in the numerous intervening steps between a current state and achieving a learning goal. Finally, individuals with brain injury spend a much larger amount of time on their own than with a therapist; thus, the importance of executive control functions translates to an individual's ability to self-teach skills and self-adjust to residual deficits of any type. Ultimately, executive control functions are crucial for independence in the community.

CASE 2 CONTINUED

The neurologist recommends that the patient work with rehabilitation therapists to train in

cognitive strategies and skills. The family is concerned because a web page from an insurance company describes cognitive rehabilitation as experimental.


- **Does current evidence support the use of cognitive rehabilitation therapy?**

A growing clinical evidence base supports the potential effectiveness of executive control and problem-solving therapies³⁸⁻⁴⁰ in individuals with brain injury. In particular, there is sufficient evidence that metacognitive strategy instruction should be a standard practice used with young to middle-aged adults with TBI who have difficulty with problem solving, planning, and organization. Metacognitive strategies involve direct instruction to teach individuals to plan and manage their goals by breaking complex tasks into steps. Immediate positive changes in functional activities and to a lesser extent in impairment level outcomes have been observed after metacognitive interventions in randomized controlled trials.⁴¹⁻⁴⁴ These and other interventions for attention, memory, and other deficits have been systematically reviewed.^{38,39,45}

- **What pharmacotherapeutic options could be considered with the goal of enhancing cognitive functioning?**


Agents that modify dopamine functioning have been used for improving aspects of cognitive functioning in patients with TBI. Bromocriptine has been recommended for use in enhancing aspects of executive functioning (eg, divided attention/central executive functions) in patients with severe TBI.^{46,47} Other agents that modulate catecholamine function, such as dextroamphetamine and amantadine, have also been used.^{46,47} However, there is less direct evidence to support positive clinical effects on executive control functions. As a general rule, dosing of agents that modulate dopaminergic function should be based on individual response, as dopamine modulation of function tends to follow a U-shaped curve that varies in dose-relationship for each individual.⁴⁸⁻⁵⁰

CASE 2 CONCLUSION

 After 3 months of inpatient rehabilitation therapy, the patient is able to return home. He is able to perform all activities of daily living as well as accomplish necessary chores such as shopping. He continues to have difficulties with more challenging problems and multitasking, but by 1 year postinjury, he is able to return to his employer doing part-time work while continuing to practice strategies he learned during rehabilitation.

MILD TBI

CASE PRESENTATION 3

 A 21-year-old college student is injured playing rugby when she is struck in rapid succession by an opposing player from the front and then another player from behind. She lay on the ground not moving for 10 seconds or so. She is then able to sit up and rise to her feet slowly and walk off the field with the assistance of a coach to steady her. She complains that her head hurts and that she feels nauseated and dizzy.

- **How is concussion severity graded?**

Concussion, a mild TBI, is defined by the American Academy of Neurology as a trauma-induced alteration in mental status (confusion and amnesia) that may or may not involve loss of consciousness.^{51,52} A standardized grading scale for concussion includes 3 grades. Grade 1 involves transient confusion, no loss of consciousness, and concussion symptoms or mental status abnormalities that resolve in less than 15 minutes. Grade 2 involves transient confusion, no loss of consciousness but concussion symptoms or mental status abnormalities that last more than 15 minutes. Any grade 2 symptoms lasting more than 1 hour suggests a need for medical observation. Grade 3 involves any LOC, whether brief (seconds) or prolonged (minutes). Common symptoms of concussion are shown in **Table 4**.

The grading scale helps to guide decision making for management of the concussed athlete. This includes determining whether and when the athlete may return to competition. Brain imaging with CT or MRI is recommended for grades 2 and 3 if symptoms worsen or persist longer than 1 week. Secondary prevention of worsened injury is an important goal. Specific guidelines for return to play have been recommended and are discussed in depth in other resources.^{51,52}


While patients with moderate to severe TBI are likely to receive medical attention, patients with mild TBI are more likely to remain undiagnosed, especially if not assessed immediately, as in the case patient.⁵³⁻⁵⁵ For less severe dysfunction, patients may have symptoms that are not recognized by health care providers without specific screening but which are significant and need to be addressed.⁵⁶

- **What is the utility of neuroimaging after mild TBI?**

The majority of patients with mild TBI will show no signs of injury on CT scan. However, a significant

minority may have signs at the time of injury, such as contusions, intraparenchymal hemorrhages, or swelling, leading to the term *complicated mild TBI*. CT is valuable for detecting or ruling out the uncommon but potentially serious and treatable subdural hemorrhage (which may occur even without LOC). Thus, a clinical definition of mild TBI does not necessarily imply lack of visible brain injury. MRI is more sensitive to soft tissue injury, including white matter injury, and residual from hemorrhages and thus it may help localize injury, determine the extent of damage, and quantify the extent of atrophy. On the other hand, a lack of findings on imaging cannot be used to rule out brain injury. Newer imaging techniques may be more sensitive to the sequelae of injury.⁵⁷

CASE 3 CONTINUED

 The patient presents to a neurologist 6 months postinjury, and she continues to complain of headaches, sensitivity to noise, irritability, and difficulty sleeping. She is having difficulty in school, finding herself unable to concentrate in class, and her grades have dropped. She is concerned that she may have “permanent brain damage.” The patient also states that she is having difficulties with attention and memory. She has been told by another physician, however, that she should not have any actual residual neurologic deficits from her mild brain injury.

- **What diagnostic term may be applied to this patient’s current constellation of symptoms?**

POSTCONCUSSIVE SYNDROME

This constellation of symptoms has been described as the postconcussive syndrome (PCS). PCS remains a somewhat difficult to define entity or group of entities, with variable presentations, sources, and possible courses. The ICD-10 definition includes a history of head trauma with LOC preceding the onset of symptoms by up to 4 weeks, with at least 3 of 6 symptom categories: (1) headaches, dizziness, general malaise, excessive fatigue, or noise intolerance; (2) irritability, emotional lability, depression or anxiety; (3) subjective complaints of concentration or memory difficulty; (4) insomnia; (5) reduced tolerance to alcohol; and (6) preoccupation with these symptoms and fear of permanent brain damage. Documentation of cognitive dysfunction on objective testing is not required for diagnosis. Although these symptoms occur, by definition, after a concussion, this does not necessarily mean that the acute brain injury directly causes these symptoms. Given the variability in symptoms and sources, it remains valuable to describe

Table 4. Common Symptoms of Concussion

Early (minutes and hours)	Headache
	Dizziness or vertigo
	Lack of awareness of surroundings
	Nausea or vomiting
Late (days to weeks)	Persistent low-grade headache
	Light-headedness
	Poor attention and concentration
	Memory dysfunction
	Easy fatigability
	Irritability and low frustration tolerance
	Intolerance of bright lights or difficulty focusing vision
	Intolerance of loud noises, sometimes ringing in the ears
	Anxiety and/or depressed mood
	Sleep disturbance
Observable features may include:	
	Vacant stare (befuddled facial expression)
	Delayed verbal and motor responses (slow to answer questions or follow instructions)
	Confusion and inability to focus attention (easily distracted and unable to follow through)
	Disorientation (walking in the wrong direction, unaware of time, date, and place)
	Slurred or incoherent speech (making disjointed or incomprehensible statements)
	Gross observable incoordination (stumbling, inability to walk tandem/straight line)
	Emotions out of proportion to circumstances (distracted, crying for no apparent reason)
	Memory deficits (exhibited by the athlete repeatedly asking the same question or inability to memorize and recall 3 of 3 words or 3 of 3 objects in 5 minutes)
	Any period of loss of consciousness (paralytic coma, unresponsiveness to arousal)

Adapted with permission from Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. *Neurology* 1997;48:581–5.

symptoms, exacerbants, and functional status on an individualized level.

- **Is additional evaluation warranted in this patient?**

The evaluation of patients who report difficulties after TBI must be individualized, and the following issues may be helpful in individual decision making. Fortunately, most patients with mild TBI improve to the point that they would describe themselves as no different from baseline. Although the recovery trajectory

for most patients who survive TBI is positive over time, there is significant variability in the rate and end point of recovery. A significant minority (10%–20%) report persistent symptoms that can last months and years postinjury, potentially contributing to a wide-ranging impact on an individual's life.^{58,59} The pathogenetic factors that lead to persistence of syndromes are controversial and poorly understood. It is not clear that imaging findings are predictive of persistence of symptoms.

A full evaluation of this patient should include determining potential contributors to the genesis or maintenance of symptomatology. These need not be directly related to acute brain injury per se, but may be issues that have arisen in the intervening time period. Differential diagnosis of some of the most common contributors includes depression, headache, neck pain, other chronic pain, and anxiety disorders, including posttraumatic stress disorder (PTSD).⁶⁰ Any of these, with associated medications or other conditions, may contribute to poor functioning, such as irritability, poor concentration, slowed cognition, and altered personality or social interactions. Note that changes in one's abilities may interact with these other issues in complex ways. Changes in sensory input, such as from reduction in hearing, may also manifest as complaints of difficulty processing information. Damage to inner ear structures may result in complaints of dizziness or imbalance. Identification of these factors may help to guide management, even while the specific attribution of symptoms to TBI per se may remain in question.

- **Are cognitive deficits important in mild TBI?**

The occurrence of cognitive deficits in moderate and severe TBI is well-recognized, but cognitive deficits may also be a significant problem after mild TBI as well. Delineation of cognitive dysfunction has been more problematic, however. Although self-reported symptoms and outcomes from cognitive testing vary greatly, dysfunction in attention, working memory, speed of processing, and executive control are commonly reported and may be the most affected domains in mild TBI.^{58,61–65} Aspects of executive control may be important factors in determining successful return to work after mild TBI.³⁴ Thus, it may be worthwhile pursuing formal neuropsychological evaluation in this individual. This evaluation would not only serve a diagnostic purpose, but may be of practical importance in planning rehabilitation, obtaining school-based assistance, or otherwise determining appropriate strategies for vocational or other goals. A major caveat is that “normal” performance on formal neurocognitive tests


does not rule out dysfunction in real-life settings for at least 2 reasons. First, scores are typically compared to a normative sample of healthy subjects, allowing a determination of how an individual performs relative to that range. Strictly speaking, a determination of postinjury dysfunction would require comparison with a baseline assessment prior to injury. Second, formal paper and pencil or computerized neurocognitive tests in a quiet, secluded testing environment may not be sensitive to the factors in everyday, complex environments that may disrupt performance in a person who is prone to distractions or disorganization.

- **What additional interventions should be offered in PCS?**

Early intervention may be one of the most important principles in management of PCS, with the goal of reducing the chances that an individual will have persistent symptoms. Even simple educational information interventions may reduce PCS symptoms.^{66,67} On the other hand, a rapid return to the high demands of work may actually impede recovery, especially if the individual faces unexpected difficulties or failures leading to frustration, anxiety, fear, or other adverse reactions. Referral for counseling and assistance with coping and adaptation may be beneficial. As mentioned above, identification of other contributors to symptomatology provide specific targets for management. It is important to watch for signs of depression and manage these proactively. Rehabilitation approaches may be beneficial for residual cognitive dysfunction.

TBI AND PROBLEMS WITH MEMORY

CASE PRESENTATION 4

 A 30-year-old former theater director presents to a neurology clinic 5 months after she was injured by a falling spotlight. She can recall driving to work on the day of the injury but has little memory of other events. During the interview, the neurologist observes that she has difficulty retaining information during the conversation and repeats questions. It is apparent that she has difficulties with learning and retrieval of new information. At baseline, she was very active socially and managed multiple concurrent events in her job. She now complains that she has difficulty keeping track of simple appointments. She also complains of difficulty following rapid conversations involving multiple people and finds herself highly distracted

in her former work environment. She is having trouble with her employers and colleagues not understanding why she continues to have difficulty months after her head injury, especially since she shows no external signs of injury. Furthermore, an initial CT scan reportedly showed no brain lesions.

The neurologist obtains an MRI, which is read as showing no focal cortical lesions and nonspecific white matter T2 hyperintensities. However, on review the neurologist notes that the ventricles and sulci appear to be larger than expected for the patient's age; he also localizes small T2 hyperintensities to deep white matter (basis pedunculi and internal capsule) as well as in subfrontal white matter structures. The patient brings the report from a neuropsychological evaluation stating that she has deficits in attention, speed of processing, and memory functioning. She asks you to explain why she might have such difficulties despite "normal" brain imaging and what she can do to improve her functioning.

- **How might this patient's injury and sources of dysfunction be characterized?**

Subjective report is not reliable for determining initial injury history, especially given issues with PTA. Without detailed records, it is more important to characterize current functioning. It is likely that this patient's injury is not limited to the visible focal lesions. The proportionally enlarged sulci argue against hydrocephalus and support ex vacuo dilatation of the ventricles. Although early imaging did not show obvious large lesions, a process of axonal and cellular degeneration may have proceeded on a much more widespread scale than apparent on early imaging. It is likely that the patient has diffuse or multifocal axonal injury. The evidence of axonal injury that is visible is likely only a small portion of actual injury. Long fibers are particularly vulnerable. Among these are fibers carrying neuromodulators in projections from the brainstem to cerebral end targets and those that connect the prefrontal cortex with other brain regions. Some of the most common deficits associated with DAI are in speed of processing, frontal executive functions, and declarative memory.²⁶

Most of the major neuromodulators of the brain are produced in small nuclei at the base of the brain or in the brain stem and projected to cerebral structures. Acetylcholine from the basal forebrain is projected to cortex throughout the brain. Dopamine from the ventral tegmental area is projected primarily to prefrontal cortex. Norepinephrine from the locus coeruleus is projected to cortex throughout the brain, as well as thalamus, cerebellum, and spinal cord. Serotonin is

also predominantly produced in brain in pons and midbrain nuclei and projected throughout the brain, with prominent targets including frontal lobes and hippocampus. On the other hand, GABA neurons are distributed throughout the brain, in particular as inhibitory interneurons. Unfortunately, it is not possible to determine the specific pharmacology of each patient with clinically available methods, but disruption in one or more of these systems may contribute to neurologic symptoms seen in TBI.

- **What pharmacotherapeutic approaches might help address this patient's cognitive deficits?**

PROCESSING SPEED


The efficiency and speed with which an individual can process information and accomplish cognitive tasks and the ability to focus attention are commonly affected by TBI. A common underlying pathophysiologic factor may be damage to interconnecting systems in the brain, as would occur with axonal injury. Practice guidelines support the use of the stimulant methylphenidate in the treatment of deficits in attention and speed of information processing following TBI.⁴⁷ The evidence for methylphenidate (0.25–0.30 mg/kg twice daily) is strongest for an effect on speed of cognitive processing and sustained attention/vigilance.^{68,69} The cholinesterase inhibitor donepezil (5–10 mg/day) has also been recommended for enhancing attention in patients with moderate to severe TBI in subacute and chronic periods of recovery. Dextroamphetamine and amantadine may also be considered.

MEMORY

Complaints of problems with memory are common after TBI, although the sources of these complaints may be varied. Delineating the specific sources may point to different strategies for management. Deficits in declarative or episodic memory may be related to damage to medial temporal structures as well as to the basal forebrain and long tracts that connect structures important for memory processing. The basal forebrain, a major source of cholinergic projections throughout the brain, is particularly vulnerable to injury, and long projections may be vulnerable to shearing injury.⁷⁰ Problems with memory encoding and retrieval may be related to attention and frontal executive functions that influence the selectivity and depth of information processing as well as the ability to organize information to be encoded and strategically retrieve information to be recalled. The cholinesterase inhibitor donepezil (5–10 mg/day) has been

recommended to enhance aspects of memory function for patients with moderate to severe TBI in subacute and chronic periods of recovery.^{47,71} Data support the use of rivastigmine for improving memory deficits as well in patients with moderate to severe memory impairment at baseline.⁷² In general, these cholinesterase inhibitors appear to be safe and well-tolerated in patients with TBI.⁷³ Methylphenidate may also improve learning and memory functioning after TBI by improving attention to information.⁶⁹

CASE 4 CONTINUED

 The patient complains that fatigue limits her work and home activities the most. Despite her high energy prior to the injury, she states that she now becomes quite fatigued when performing any of the minor problem-solving activities she once did easily at work. She complains that a small amount of difficult thinking is more fatiguing than physical exertion.

POSTINJURY CENTRAL FATIGUE

Fatigue is likely the most common symptom after TBI, reported in 21% to 73% of patients with TBI.^{74,75} There is no standard definition of fatigue, but the key elements include a requirement for increased effort to maintain mental activities and difficulty sustaining goal-directed efforts.⁷⁶ Central fatigue is the major concern in TBI and should be distinguished from peripheral fatigue, which refers to muscular or other sources outside the brain. Fatigue affects functional recovery, emotional well-being, cognitive functioning, quality of life, and ability to perform daily activities.


Assessment of fatigue must take into account its dynamic nature, including fluctuations and the contexts in which an individual functions. A key goal of the assessment is to determine potential contributors to fatigue, as these may be targets for management. These may include, but are not limited to, sleep dysregulation, pain, emotional distress, lack of physical exercise, and medications. Available standardized questionnaires may be helpful in characterizing an individual's fatigue.

- **What strategies are recommended for management of fatigue?**

Regular physical exercise is a key recommendation. Adherence to an exercise regimen may be improved by individualizing the activities based on personal interests and limitations. Creativity and problem-solving may be required, and professional consultation with physical therapists, recreational therapists, or personal trainers may help in this regard. Compensatory strategies to manage energy use may be helpful for a person to achieve

desired functional goals given limited capacity for activity. The patient may require assistance identifying situations or behaviors that exacerbate fatigue that could be modified. Addressing sleep disturbances is an obvious and crucial step to improving energy levels. Sleep history and in some cases polysomnography may help diagnose sleep disturbances. Medications such as β -blockers, antiparkinsonergics, and antiepileptics may contribute to feelings of tiredness. Reduction of distractions, thereby reducing the amount of cognitive effort required to accomplish tasks, may be beneficial. Pharmacotherapy with agents that improve attention and concentration, such as psychostimulants, may be helpful. Modafinil is a newer agent that promotes alertness. Activating antidepressants, such as venlafaxine or duloxetine, also may be helpful.

CASE 4 CONTINUED

 As the patient approaches age 55 years, her spouse complains that her memory seems to be worsening. She has a family history of Alzheimer's disease (AD), but her father did not develop problems until age 70 years. The patient's spouse asks if she could be developing AD.

- **What steps should be taken to manage this patient's reported cognitive decline?**


TBI AND AGING

Individuals with TBI may be at higher risk for age-related decline in functioning, which highlights the fact that TBI is not simply an acute disorder. For example, the risk of developing AD may be increased 2.3 to 4.5 times in patients who suffered moderate or severe TBI.⁷⁷ Those with certain apolipoprotein E genotypes may be at greater risk.^{78,79} It is not yet clear if the features of AD after TBI are different from AD in other circumstances.

Neuropsychological testing should be obtained to determine the features of the patient's cognitive functioning. Neuroimaging should be obtained to rule out other causes of cognitive decline, including strokes, hydrocephalus, and subdural hematoma, as well as assess localization of possible progressive atrophic changes. Other potentially reversible causes of cognitive decline should be ruled out (eg, B₁₂ deficiency, thyroid dysfunction, medication side effects, depression). If evaluation reveals only age-related decline superimposed on prior TBI, then follow-up neuropsychological testing is indicated to determine the progression of dysfunction. Regular physical exercise and pharmacotherapy with cholinesterase inhibitors or memantine may slow progression of cognitive decline.

COMBINED COMBAT NEUROTRAUMA

CASE PRESENTATION 5

 A veteran returning from active duty in the Middle East who presents to a neurologist for evaluation states on a screening questionnaire that he was exposed to blasts and head injuries in combat. In one incident, while he was riding in a convoy, his truck was struck by a blast from a roadside improvised explosive device. A wheel was caught in the crater and the vehicle dove into a ditch. He states “I think my head struck the side of the truck, and I may have blacked out—I’m not sure how long.” He reports having felt dazed and somewhat confused. This seemed to resolve within a day, and the soldier returned to active duty. However, he was exposed to several more blasts during his tour. While he cannot recall the details of each incident clearly, he denies loss of consciousness but endorses feeling dazed with each episode. He complains that he experienced the most difficulty once he returned home. He experienced trouble getting organized for job applications. “I would get started, but then I always ended up doing something else,” he reports. Others describe him as irritable and easily angered. He feels depressed and avoids leaving his home. The patient also describes feelings of constant distress and episodes where he feels panicked. These feelings are worsened by being in public spaces as well as sudden honking or noises while driving.


EPIDEMIOLOGY

This individual’s experience is common among veterans who have served in combat. Recent combat-related activities in the Middle East have resulted in an increased incidence of TBI, and TBI has been called a hallmark injury of current combat activities.⁸⁰ The Department of Defense has estimated that over 27,000 military service members were diagnosed with TBI in 2008.⁸¹ It is estimated that 59% of soldiers exposed to blasts will have some form of closed head injury,⁸⁰ although head injury is commonly caused by other combat and non-combat-related causes, such as motor vehicle collisions, falling objects, altercations, or projectile strikes to helmets. According to Walter Reed’s Brain Injury Center, 31% of battle-injured soldiers admitted between January 2003 and April 2005 had TBIs. Within the VA Medical Centers, brain injury is a leading contributor to increasing health care cost due to chronic treatment requirements of afflicted veterans.⁸²

- **How can the severity of injury be rated for this patient?**

Traditional approaches to rating severity may not be valid in combat-related injury. In this case, there are no GCS or PTA scores to rate severity. It is not yet clear how the effects of a blast should be rated, nor how comparable blast effects are to nonblast severity ratings, as pathophysiologic effects of blast are not yet fully understood. Multiple exposures may be an important factor, possibly leading to injury more severe than is obvious from reported duration of LOC; however, the effects are not yet fully understood. Characterizing current functioning will provide more important guidance for management.

CASE 5 CONTINUED

 The neurologist determines that the patient has functional difficulties referable to executive control dysfunction. However, his overall level of functioning seems to be much worse than directly explained by his cognitive abilities per se.

- **What neuropsychiatric comorbidities may contribute to poor functioning in individuals with TBI-related cognitive dysfunction?**

Individuals who have suffered TBI are at high risk for other neurobehavioral disorders, including depression, anxiety, and PTSD. PTSD symptoms may interact with TBI, and these conditions should be evaluated and managed in combination. Symptoms of distress, anxiety, and panic that are common with PTSD may be particularly poorly controlled with concomitant TBI. Mental health professionals familiar with PTSD should be involved at an early stage. Individuals who have suffered TBI are at high risk for depression. This may be related to biological factors as well as to difficulties with adjustment to disability, social and occupational changes, and experiential trauma. Anxiety occurs frequently after TBI and may become manifest in symptoms of fear, apprehension, and distress as well as discrete episodes of panic. Anxiety may also be a core component of PTSD following the trauma that induced the TBI. Finally, irritability, low frustration tolerance, “bad temper” and even explosive behavior are major sources of functional disablement after TBI. These may also be features of PTSD, and the interaction with TBI is not yet fully understood.

- **What therapeutic options could be discussed with this patient?**

There is insufficient evidence to support specific guidelines for pharmacotherapy of depression in TBI. Tricyclic antidepressants are supported by some limited clinical evidence; however, clinicians must be cautious of potential anticholinergic side effects, including clouding of cognition. Selective serotonin-reuptake inhibitors

(SSRI) or newer mixed serotonin-norepinephrine-reuptake inhibitors (SNRIs) are also reasonable options. These agents may also be helpful with the stabilization of emotional dysregulation.


Nonpharmacologic approaches to depression are vital to effective management. All patients should be offered counseling services to assist with coping and adjustment after TBI. Cognitive behavioral therapy and psychotherapeutic approaches may be helpful in treatment of depression.

There is insufficient evidence to support specific recommendations for pharmacotherapy of anxiety after TBI; however, medication options to consider include SSRIs or SNRIs. Benzodiazepines have long been used to treat anxiety symptoms but are potentially problematic due to issues with sedation, cognitive impairment, and potential for habituation, dependency, and abuse. Furthermore, it is commonly suggested that patients with TBI may be more sensitive to the side effects of psychotropic medication treatment, although direct evidence is lacking.⁸³ These increased side effects include but are not limited to potentially worsened cognitive dysfunction or imbalance on many medications, or seizures on medications that may lower seizure thresholds (eg, tricyclic antidepressants).

Emphasis on nonpharmacologic approaches would generally be preferable, where possible. Cognitive behavioral therapy for anxiety is supported by clinical trials in patients with mild and moderate TBI, with documented improvements in generalized anxiety symptoms as well as PTSD.⁸⁴

Directly addressing issues of irritability, low frustration tolerance, “bad temper,” and explosive behavior through counseling, efforts to improve self-awareness, and training in improved self-regulation may be helpful. Although practice guidelines support the use of β -blockers for the treatment of aggression following TBI using propranolol or pindolol,⁴⁷ it is less clear whether β -blockers would be helpful for less severe disturbances. In addition, β -blockers may dull cognition and exacerbate depression. SSRIs such as sertraline and paroxetine may assist with stabilizing behavior, and are among the best choices in those with depression, anxiety, and emotional-behavioral lability. Valproate, lithium, and tricyclic antidepressants are also options.


CASE 5 CONCLUSION

 The symptoms of anxiety and behavioral lability improve over time with active efforts on the part of the patient and pharmacotherapy. Through rehabilitation, the patient is able to apply strategies for improving his learning, organization, and planning. He

is able to enroll in college and obtain a bachelor's then master's degree before joining the work force.

LATE COMPLICATIONS OF TBI: HYDROCEPHALUS

CASE PRESENTATION 6

 A 35-year-old teacher is participating in physical therapy for hemiparesis after suffering a TBI while skydiving several months ago. Records from the initial injury describe frontal and temporal contusions and ventricular hemorrhage. During the second month postinjury, the patient begins responding more slowly to questions and becomes less likely to participate with therapy, seeming apathetic. His balance appears to worsen, although mainly his gait speed slows down and he tends not to lift his feet off the ground while walking. However, his strength is not diminished.

A CT scan shows an increase in ventricular size compared with prior scans. Ventricles are enlarged out of proportion to the width of the sulci, and periventricular tissue appears hypodense.

DIAGNOSIS AND TREATMENT

Hydrocephalus is the most common neurosurgically treatable complication during rehabilitation of TBI.⁸⁵ Classic symptoms include cognitive slowing, reduced attention, poor initiation, gait apraxia, and urinary incontinence, all consistent with frontal-subcortical dysfunction. TBI, especially with subarachnoid or intraventricular hemorrhage or meningitis, increases the risk of developing hydrocephalus. Late hydrocephalus should be considered in the differential diagnosis when a patient seems to slow or worsen during rehabilitation, even if the classic triad is not present. Differential diagnosis considerations should include depression, chronic subdural hematoma, seizures, central nervous system infection (eg, meningitis), medication effects, sleep disturbance, and other systemic metabolic or infectious disturbances. Diagnostic evaluation should include imaging with CT or MRI. Increased ventricular size is not a clear indicator of hydrocephalus; however, ventricular enlargement is common after more severe TBI, likely due to atrophy.⁸⁶ In most cases after TBI, the hydrocephalus is communicating so that ventricular enlargement is seen to affect all the ventricles. Ventricular hemorrhage is a risk factor for hydrocephalus.

Hydrocephalus can have a significant effect on recovery of function, possibly resulting in not only slowing of recovery but also regression. Treatment can have a dramatic effect. The most effective long-term treatment

is surgical placement of a shunt. The decision-making process for shunt placement is complex. Periventricular lucency on CT or T2 hyperintensity on MRI as well as smaller sulci (rather than enlarged sulci in atrophy) indicate a greater likelihood of shunt-responsive hydrocephalus.^{87,88} These findings likely reflect transependymal fluid movement. However, complications of shunt placement are frequent and can include shunt failure, infection, subdural hematoma, seizures, and overdrainage. If a shunt is placed, continued vigilance is necessary to detect these complications.

CONCLUSION

As acute care for TBI continues to improve, more individuals will survive and progress through stages of postinjury recovery. Neurologists will play an increasingly important role not only in managing basic neurologic complications, but also in bridging neuroscience and rehabilitation to optimize functional recovery after injury.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic. Go to www.turner-white.com and select Neurology from the drop-down menu of specialties.

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