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Neuropsychiatry and Traumatic Brain Injury

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Introduction

Although the earliest descriptions of brain injuries date back to the ancient Egyptians (1700 B.C.) where 27 cases of head trauma are recorded in *The Edwin Smith Surgical Papyrus,* the neuropsychiatric concept that behavioral sequelae can result from brain injury was not understood, as this culture believed that the heart was the seat of emotion and thinking (Finger, 2000). Later on in the historical timeline, there appears to be some hint of recognition that the brain and human behavior may be linked when in 400 B.C., the Greek physician Hippocrates wrote *On Injuries of the Head* and described a patient with head trauma who subsequently experienced delirium and seizures (Hippocrates). More recently in 1848, the now well-known case of Phineas Gage, who suffered destruction of the left frontal lobe of his brain while at his job laying down track for a new railroad, was documented. Subsequent to his injury, he evidenced a change in personality marked by impulsivity and poor judgment. He was unable to resume his occupation where he had previously been highly regarded, as his colleagues noted, "He was no longer Gage." This landmark case in our modern era linked Gage's brain trauma as being etiologically responsible for his emotional changes (Barker, 1995). Subsequently, others such as Adolf Meyer in 1904, proposed that brain trauma from a variety of causes could lead to neuropsychiatric syndromes such as delirium, psychosis, memory problems, and mania, and he introduced the nosology "post-traumatic insanity" to try to define this phenomenon more precisely (Meyer, 1904). More recently, in 1972, the neuropsychologist Dr. Luria described the case of a Russian soldier, Leva Zasetsky, who had suffered a bullet wound to the left parieto-occipital area of his brain during combat in World War II. Dr. Luria worked with him for 25 years and recorded this patient's courageous struggle to recover some of his ability to function despite cognitive deficits and frightening hallucinations (Luria, 1972).

In the United States, about 2 million patients sustain head trauma each year due to vehicular accidents, falls, violence, or sports injuries (NIH Consensus Development Panel, 1999). Due to improved acute trauma care in hospitals, many patients survive the physical ravages of traumatic brain injury (TBI) but many subsequently experience neuropsychiatric disorders such as those described in the

patients above. In this chapter, the modern neuropsychiatrist's role in the diagnosis and treatment of the psychiatric consequences of TBI such as mood and anxiety disorders, psychosis, agitation, arousal and attention, dementia, and sexual dysfunction will be reviewed.

Depression

Hopelessness and sadness are characteristic of the emotional state known as depression, which is a commonly observed neuropsychiatric condition after TBI. The psychiatrist's handbook, known as the *Diagnostic and Statistical Manual Text Revision* (DSM-IV-TR) (American Psychiatric Association, 2000), outlines the necessary symptoms which a patient must experience to be diagnosed with major depression. These include a depressed mood or loss of pleasure for 2 weeks, as well as the presence of four or more of the following symptoms: change in appetite or weight loss, insomnia or hypersomnia, fatigue or loss of energy, being restless or slowed down to a degree that is observable by others, feeling worthless, being unable to concentrate, or having suicidal thoughts, plan or attempt. However, patients suffering from various medical conditions such as TBI can have a prominent disturbance in their mood marked by many of the above characteristics and yet not fulfill the criteria for major depression. Such a patient would be categorized by DSM-IV-TR (American Psychiatric Association, 2000) criteria as having a mood disorder secondary to a general medical condition (TBI). In using this symptom profile, a study of 666 outpatients with TBI found that the three symptoms which most differentiated depressed from nondepressed patients were feeling hopeless, feeling worthless, and having difficulty enjoying activities (Seel et al., 2003).

The occurrence of depression after TBI has been estimated to be between 6% and 77% (Jorge & Robinson, 2003). Various methodological factors have been suggested to explain the wide range in statistics, including how the sample was chosen (i.e., referral to a specialty TBI clinic or a community population study); size of the sample (small or large); what subgroup of patients was assessed (i.e., mild, moderate, or severe TBI patients or some combination thereof); when studies were done in relation to injury (i.e., in the first few months after the incident or years or even decades later); what type of assessment tool was utilized (patient self-report questionnaire, family's report of the patient, or a clinician's structured diagnostic interview) (Newburn, 1998); and the medication status of patients at the time of the assessments (i.e., the effect narcotics, steroids, or benzodiazepines may have had on the rating of symptoms) (O'Donnell et al., 2003). Moreover, the diagnostic process is further complicated by the overlap between the two syndromes in that certain symptoms such as sleep and appetite changes as well as psychomotor agitation have been argued to be neurologic sequelae of the TBI itself, rather than the result of depression as a primary mood disturbance (Babin, 2003; Moldover et al., 2004).

Despite these issues in research protocols, what is significant in terms of clinical outcomes is that the risk of depression has been reported to remain elevated

for decades following brain injury, as was highlighted in two recently published studies. In the first, the lifetime prevalence of major depression 50 years after closed-head injury for 520 veterans who had sustained TBI during World War II was noted to be 18.5%, while a current diagnosis of major depression was recorded in 11.2% of those same veterans (Holsinger et al., 2002). The second report of 60 patients who had been followed for 30 years post-TBI recorded a lifetime rate of major depression of 26.7%, with 10% having current illness at the time of the study (Koponen et al., 2002). However, a more recent report of TBI patients noted a decline in the frequency of psychiatric disorders over time, challenging the conclusion that the rate of psychiatric diagnoses, including depression, remains elevated years later. The researchers suggest that using cross-sectional, longitudinal, and cross-sequential assessments, where age and time post-injury are controlled for at enrollment to the study, may help to improve the accuracy of the epidemiological data in future studies with this population of patients (Ashman et al., 2004).

Several factors which have been suggested as being correlated with the development of depression after TBI include lesion location (left dorsal lateral frontal lesions and/or left basal ganglia lesions, as well as possibly parietal-occipital and right hemispheric lesions), poor social functioning (less than high school education, unstable employment, and relationship difficulties), and previous psychiatric history (depression and substance abuse) (Federoff et al., 1992; Gomez-Hernandez et al., 1997; Dikmen et al., 2004; Fann et al., 2004; Jorge et al., 2005). Since major depression among survivors of TBI is associated with diminished quality of life and poorer psychosocial functioning in studies which have examined patients in both the acute and chronic phases of TBI, the need for early recognition and treatment interventions in this patient population is a pressing one (Rapoport et al., 2003; Underhill et al., 2003; Hibbard et al., 2004).

Assessment

Assessing a patient begins with the taking of a thorough history to explore the details of the TBI incident and the subsequent treatment and hospital course which took place in the acute care setting. Past and present medical history other than TBI should be reviewed, as the clinician must consider the possibility that medical co-morbidity such as epilepsy, stroke, brain tumors, infections, endocrinologic disorders (thyroid, adrenal, and pituitary), systemic neoplasms, and cardiac or renal disease may be relevant and play a contributory role in the patient's presentation of depression. For example, a common co-morbid medical problem in TBI survivors which impacts on mood is hypopituitarism, especially growth hormone deficiency; with hormone replacement therapy, significant improvements in depression, anxiety, and fatigue have been observed (Popovic et al., 2005). A review of the patient's and his family's psychiatric history are key areas to explore, since other psychiatric disorders such as bipolar illness, anxiety syndromes, adjustment disorders, and substance abuse/dependence can either produce overlapping symptoms or be co-morbid with depression; this was observed in a recent study, where 76.7% of patients with TBI and depression also met criteria for a co-morbid anxiety

disorder (Jorge et al., 2004). Pain and sleep problems are often present in TBI patients and can greatly affect mood, so a thorough assessment of these issues should also be explored when considering a possible diagnosis of depression (Branca & Lake, 2004; Oellet et al., 2004). The current medications taken by the patient must be reviewed, since many pharmacologic agents such as anticonvulsants, cardiac medications, steroids, hormones, and psychiatric medications can cause depression as a side effect. Of paramount importance to the history is an in-depth review of the patient's use of alcohol or illicit substances, as they too can play a role in the manifestation of depressive symptoms. Questions about psychosocial factors such as education, occupation, sexual history, current relationships, and avocations help the clinician to have a more complete portrait of the person as a human being, and not just a patient with TBI. To be thorough, the clinician should speak to the patient's family or friends to corroborate the history provided by the patient, so that the most accurate information guides the workup and treatment (Sadock & Sadock, 2005). Additionally, during the initial assessment process, the neuropsychiatrist should seek to communicate with other members of the treating team to discuss their observations of the patient as this may help the clinician to clarify diagnostic issues. Furthermore, this liaison approach is important in promoting a dialogue between the disciplines in order to enhance the patient's treatment as he or she progresses in the recovery process.

Pertinent to the differential diagnosis of depression in TBI patients is the syndrome of apathy (Andersson et al., 1999; Marin & Wilkosz, 2005). Symptoms such as lack of concern, emotional indifference, and reduced initiation and productivity can be assessed using the Apathy Evaluation Scale (AES) (Marin et al., 1991) in order to help differentiate mood disorder (depression) from motivational syndrome (apathy). In a recent study of 59 TBI patients, the prevalence of apathy without concomitant depression was reported to be 10.84% (Kant et al., 1998), whereas in two studies by Andersson and colleagues (Andersson et al., 1999; Andersson & Bergedalen, 2002), the prevalence of apathy in TBI patients using the AES was greater than 60%. Even across cultures, the concept of motivational deficits has been found to be a relevant construct, as was demonstrated in a later study of 80 TBI patients in a nonindustrialized country where the incidence of apathy as measured by the AES was reported to be 20% (Al-Adawi et al., 2004). Anatomically, apathy has been associated with dysfunctional activity in subcortical-frontal circuits which involve the basal ganglia, limbic structures, anterior cingulate, and prefrontal cortex (Masterman & Cummin, 1997).

In contrast to apathy, which is marked by emotional indifference, the clinician who is assessing for mood disorders should also be aware of patients with TBI who can exhibit uncontrollable outbursts of pathological laughing or crying (PLC), also known as emotional incontinence or pseudobulbar affect. These involuntary episodes are triggered by trivial stimuli which ordinarily would not result in such an extreme affective response (Zeilig et al., 1996). Since the patient's prevailing mood is neither one of depression nor euphoria, these incongruent responses can be a source of embarrassment. In a recent study, the prevalence of PLC was recorded as 10.9% during the first year after TBI (Tateno et al., 2004). Neuroanatomically,

while brainstem nuclei mediate the acts of laughing and crying by integrating facial and respiratory functions, the motor cortex exerts control over the expression of these emotions. Therefore, a lesion along the pyramidal tracts between these brain regions can result in PLC (Wilson, 1924). An alternative hypothesis to account for PLC is that there is disruption of the cerebro-ponto-cerebellar pathways (Parvizi et al., 2001).

Subsequent to the history, the clinician performs a complete physical and neurologic exam, including a cognitive assessment which reviews orientation, attention, memory, language skills, visuospatial abilities, praxis, and frontal lobe tasks. During the psychiatric mental status exam, appearance, attitude, speech, motoric abnormalities (such as tremor), mood, psychotic symptoms (such as paranoia and hallucinations), homicidality (aggressive tendencies), and suicidality are assessed. This last entity must be emphasized, as a recent epidemiologic population study of TBI patients noted that the rates of death by suicide of these patients is between 2.7 and 4.1 times that of the general population (Teasdale & Engberg, 2001). Moreover, this same research indicated that the risk of suicide remained constant over the 15-year period that these patients were followed, highlighting the fact that suicide is not just an acute problem in the first few months subsequent to a devastating injury. When the three factors of hopelessness, suicidal ideation, and suicide attempts are present, the risk of suicide is increased, as was noted in another study of 172 TBI outpatients, whose post-injury suicide attempt rate over a 5-year follow-up period was 17.4% (Simpson & Tate, 2002). In more current research, patients who had a history of TBI, as well as a diagnosis of either major depression or bipolar disorder and suicidal behavior, were more likely to be males, to have a history of substance abuse, to be aggressive and hostile, and to have been diagnosed with narcissistic, borderline, antisocial, or histrionic personality disorders (Oquendo et al., 2004). After this thorough evaluation, the neuropsychiatrist may order appropriate lab tests based on his/her findings, such as a complete blood count (CBC), electrolytes, endocrine panel, electrocardiogram (EKG), electroencephalogram (EEG), and brain imaging to help clarify the diagnosis of depression.

Treatment

Drug treatment for depression in TBI patients is based on good clinical judgment, experience with psychotropic medications in other neurologic disorders, as well as limited studies and case reports on these agents in the TBI population. Pharmacotherapy should be administered at the lowest effective doses initially with gradual increases as clinically indicated, with the goal being to ameliorate target symptoms and to minimize troublesome side effects which can interfere with rehabilitation efforts and wreak havoc on the patient's quality of life. One option for treatment is the administration of tricyclic antidepressants (TCAs), which block the reuptake of norepinephrine and serotonin into the presynaptic neuron; examples of these drugs include amitriptyline (Elavil), nortriptyline (Pamelor), and desipramine (Norpramin). The latter drug was utilized in a small blinded, randomized, placebo-lead-in study and showed efficacy in improving symptoms of depression

in ten patients with TBI (Wroblewski et al., 1996). Side effects of the TCAs include cardiac arrhythmias, sedation, and anticholinergic effects, such as dry mouth, confusion, and urinary retention. There is a potential for these medications to lower the seizure threshold, and therefore, in patients with TBI who are already at risk for this complication, vigilance in using the lowest doses possible should be the rule.

A newer class of antidepressant medications known as the SSRIs, which selectively inhibit serotonin reuptake by presynaptic neurons, includes fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), and paroxetine (Paxil); these provide another treatment choice. There are open-label studies and case reports of TBI patients whose depression improved when they were treated with the first three agents (Cassidy, 1989; Horsfield et al., 2002; Fann et al., 2000; Turner-Stokes et al., 2002; Perino et al., 2001), but there is a lack of rigorous double-blind, placebo-controlled studies using SSRIs. Recently, however, a 4-week double-blind parallel group trial with ten patients in each arm of the study was conducted involving sertraline, the stimulant methylphenidate (Ritalin) (see section below), and placebo which indicated that depressive symptoms in TBI patients improved significantly with either agent as compared to the placebo group (Lee et al., 2005). Of note, the SSRI class of medications has also been used successfully to treat PLC (Tateno et al., 2004; Muller et al., 1999). Side effects of SSRIs include diarrhea, nausea, vomiting, insomnia, sedation, tremors, and sexual dysfunction. The lack of cardiac side effects, a lower risk of inducing seizures, and fewer anticholinergic side effects makes this class a more attractive choice.

Venlafaxine (Effexor), which inhibits both serotonin and norepinephrine reuptake, has been reported anecdotally to be useful in treating depression in TBI patients. Nausea, constipation, dry mouth, and hypertension can be observed as side effects (Rao & Lyketsos, 2002). In one study there was limited evidence to recommend the treatment of TBI patients with phenelzine (Nardil), a member of the monoamine oxidase inhibitors (MAO-Is), a class of antidepressants which block the catabolism of norepinephrine and serotonin (Saran, 1985). However, with the risk of a hypertensive crisis if dietary sources of tyramine in foods such as cheese and wine are consumed, these agents are best avoided in TBI patients. Another agent, bupropion (Wellbutrin), which acts to increase the efficiency of the noradrenergic neurotransmitter systems, may be utilized in patients who have depression marked by apathy, but the risk of seizures at higher dosages of this medication makes it a less attractive choice in TBI patients (Shaughnessy, 1995).

If medications are not successful in treating depression, then electroconvulsive therapy (ECT), a nonpharmacologic option, is an alternative, as has been shown in a few case reports of TBI patients. A main concern with this therapy is that it can cause cognitive side effects which can be an issue for a TBI patient. However, the use of unilateral rather than bilateral electrodes may help to diminish this side effect (Ruedrich et al., 1983, Crow et al., 1996). Since TBI patients require support and education in order to help them cope with their injuries, psychotherapy as a treatment option for patients with depression and TBI cannot be overemphasized (Prigatano, 1991). Comprehensive neuropsychological rehabilitation programs which provide psychotherapy and cognitive remediation help to decrease

symptoms of depression and anxiety in TBI patients, as has been recently demonstrated in a single-blind randomized controlled study (Tiersky et al., 2005). This topic is discussed in depth in the chapter on counseling patients with brain injury.

A related issue in the pharmacologic treatment of depression is that of sleep disturbance. The latter problem can be present as a symptom of depression or anxiety, but alternatively it can be due to a lesion in the neuronal pathways involved in regulating the sleep–wake cycle, a result of pain from the injury, or a medication side effect. If the sleep disturbance is due to depression, then sleep will likely improve when the patient is treated with one of the above-discussed antidepressant agents. However, if sleep problems persist because of other etiologies, it is recommended that adjustment of the patient's environment and sleep patterns be implemented and a trial of an agent such as trazodone (Desyrel), a relatively specific inhibitor of serotonin reuptake, be used. An important side effect to monitor with this medication is orthostatic hypotension. Hypnotics such as benzodiazepines (BZDs) (e.g., lorazepam [Ativan]) which broadly enhance gamma-aminobutyric acid transmission, and non-benzodiazepines (e.g., zolpidem [Ambien]) which are selective BZD agonists, are best avoided due to side effects such as confusion, sedation, unsteady gait, and dependence issues (Oellet et al., 2004).

In patients with a predominant clinical picture of apathy rather than depression, medications which target the dopamine pathways in the brain should be utilized, since a disruption of dopamine transmission is implicated in the etiology of amotivation. Psychostimulants, which cause the release of catecholamines such as dopamine and norepinephrine from presynaptic neurons, have demonstrated benefits with regard to mood, cognition, and motivation in TBI patients, as has been noted in placebo-controlled studies of methylphenidate (Gualtieri & Evans, 1988; Plenger et al., 1996), as well as a chart review of dextroamphetamine (Cylert) (Hornstein et al., 1996). Side effects can include psychosis, anxiety, irritability, insomnia, and increases in heart rate and blood pressure. The potential for an increased rate of seizures, while present, has been uncommon clinically. Other agents which augment dopaminergic transmission and can be used in this population of patients, include amantadine (Symmetrel) (Nickels et al., 1994; van Reekum et al., 1995; Kraus & Maki, 1997), levodopa/carbidopa (Sinemet) (Lal et al., 1988), bromocriptine (Parlodel) (Muller & Von Cramon, 1994; Powell et al., 1996), and selegiline (Eldepryl) (Newburn & Newburn, 2005). Psychosis, gastrointestinal side effects and orthostatic hypotension can occur with these medications. Another option for patients with TBI and apathy is modafinil (Provigil), which promotes wakefulness and is approved for narcolepsy, but whose exact pharmacologic mechanism of action is unknown. It has shown the potential for increasing alertness and attention and improving cognition in an open-label trial of ten TBI patients (Teitelman, 2001). The most common side effect of modafinil is headache, but nausea, vomiting, and anxiety can also occur.

In addition to disruption of dopamine transmission in apathy, there is evidence to suggest that dysfunction of the cholinergic system can also lead to amotivation. This is based on the research done in Alzheimer's dementia (AD): patients with

AD are often apathetic, while biochemically they suffer from a deficiency of the neurotransmitter acetylcholine. Neuroanatomically, in both TBI and AD, cholinergic limbic–neocortical connections which are damaged can cause interference in the integration of cognitive and emotional processes (Cummings & Back, 1998). Therefore, cholinergic agents such as acetylcholinesterase-inhibitors (AchE-Is) which temporarily disrupt the hydrolysis of acetylcholine and thus increase its concentration in the synapse, have been shown to be beneficial in improving apathy in AD patients (Cummings, 2000). With this rationale, it was demonstrated that in one uncontrolled trial of four TBI patients in which the AchE-I donepezil (Aricept) was used, apathy scores on a structured rating scale improved (Griffin et al., 2003). Side effects of the AchE-Is include nausea, vomiting, and diarrhea. A patient example is provided to highlight some of these clinical issues.

A 53-year-old female was found unconscious at the bottom of a staircase in her home. In the emergency department, a head computerized tomography (CT) revealed an epidural hematoma of the right frontal-temporal region as well as bilateral frontal contusions. Several months later during her rehabilitation at a TBI unit, she was noted by the therapists working with her to have frequent crying spells and to be despondent over her cognitive deficits. During sessions she was often amotivated, displayed poor self-esteem, and complained of low energy and difficulty with concentration. After neuropsychiatric assessment, this patient was diagnosed with depression secondary to TBI, as the rest of the medical workup was negative. She was treated with an SSRI with improvement of her tearfulness, overall mood, and a notable increase in her participation in her rehabilitation classes.

Mania

After TBI, patients can experience an elevated mood state which is referred to as mania. In DSM-IV-TR (American Psychiatric Association, 2000) nosology this is defined as an elevated, expansive, or irritable mood which lasts at least 1 week. When the patient has an elevated mood, three of the following symptoms must also be present to make the diagnosis of mania, while when an irritable mood predominates, four additional symptoms are required. These include inflated self-esteem, decreased sleep, pressured speech, racing thoughts, poor attention, an increase in goal-related activity, and excessive involvement in pleasurable activities (e.g., spending sprees or sexual indiscretions) which could have painful repercussions. DSM-IV-TR (American Psychiatric Association, 2000) diagnostic categorization would classify such a patient as having bipolar I disorder. However, patients suffering from various medical conditions such as TBI can have an expansive or irritable mood and yet not meet full criteria for a manic episode or bipolar disorder. In such a case, mood disorder secondary to a general medical condition would be the diagnosis given. Secondary mania is a concept similar to the preceding one, and was first described by Klerman and Krauthammer (1978), who observed patients without previous psychiatric history who developed a psychotic disorder after a medical illness. Their definition of this syndrome included an elated or irritable mood in addition to only two of the above listed criteria.

The occurrence of mania after TBI has been estimated to be far less frequent than depression, in the range of 1.6–9% (Silver et al., 2001; Jorge et al., 1993). A recent study of 60 patients followed 30 years post-TBI revealed only one patient (1.7%) with a diagnosis of bipolar II disorder (Koponen et al., 2002), which by definition is an episode of depression and, at some time, an episode of hypomania (same symptoms as mania but the duration is at least 4 days but less than 1 week) (American Psychiatric Association, 2000). Although it is less likely to occur, some TBI patients have also been observed to experience rapid-cycling bipolar disorder in which at least four manic, hypomanic, or depressive episodes occur within 12 months (Monji et al., 1999; Murai & Fujimoto, 2003). Anatomically, an association has been made in TBI patients suffering from symptoms of mania and lesions which occur mainly in the right basotemporal or orbitofrontal regions (Jorge et al., 1993; Starkstein et al., 1988). However, several new case studies have noted TBI patients suffering manic episodes after left frontal or bilateral temporal lesions (Heinrich & Junig, 2004; Mustafa et al., 2005).

Assessment

When obtaining the history, the clinician should consider other medical conditions (in addition to TBI) which could present with symptoms of mania, such as epilepsy, brain tumors, central nervous system infections, thyroid disease, renal disease, and vitamin deficiencies. Other psychiatric illnesses to be screened for include substance abuse, since manic symptoms can be observed in patients who use opioids, hallucinogens, and cocaine. Diagnoses such as borderline or antisocial personality disorders also need to be considered since overlapping features of these syndromes such as irritability, aggressiveness, and impulsivity can mimic the manic state (Sadock & Sadock, 2005). Obtaining a list of medications, including over-the-counter preparations is essential, since agents such as antidepressants, steroids, and herbal preparations such as St. John's Wort and ginkgo biloba can precipitate manic symptoms as was reported in a recent case study of a TBI patient (Spinella & Eaton, 2002). The clinician's observations and findings after taking a careful history and neuropsychiatric evaluation (as outlined in the previous section on depression) will guide the ordering of appropriate tests such as brain imaging, lab tests, or EEG to further clarify the diagnosis.

Treatment

With the completion of this workup, the neuropsychiatrist is left with the decision of choosing an appropriate agent to treat the manic symptoms experienced by TBI patients. The literature in this area is sparse as there are no double-blind randomized placebo-controlled studies. Instead, clinical judgment is guided by the treatment of classical bipolar disorder and case reports of patients with TBI (Kennedy et al., 2001). Anticonvulsants such as valproic acid (Depakote) and carbamazepine (Tegretol) have been used successfully in the treatment of the TBI manic patient and may be particularly good options if there is the presence of a

seizure disorder as well (Monji et al., 1999; Pope et al., 1988; Stewart & Hemsath, 1988; Sayal et al., 2000; Kim & Humaran, 2002). Side effects of the former agent include weight gain, thrombocytopenia (low platelet count), and hepatic dysfunction while the latter can cause hyponatremia (low serum sodium) and hematologic dysfunction. Other anticonvulsants such as lamotrigine (Lamictal) and topiramate (Topamax) have also been shown to successfully treat bipolar disorder but there have been no studies which have used these agents in patients with TBI and mania (Calabrese et al., 1999; Marcotte, 1998). Side effects of lamotrigine include dizziness, sedation, ataxia, and most importantly, rash, which can then evolve into the potentially fatal condition known as Stevens–Johnson syndrome. Adverse effects of topiramate include sedation, decreased appetite, speech disorders, and cognitive impairment. Gabapentin (Neurontin) may also be a reasonable choice to treat manic symptoms based on its use in agitation with other types of neurologically impaired patients (Roane et al., 2000). However, as with the other pharmacologic agents already described, there are no controlled studies of its use with TBI patients. Common side effects of gabapentin include fatigue and dizziness. Although the mood stabilizer lithium (Eskalith) is used in classical bipolar disorder with much success and has been recommended for mania in relation to TBI, much caution must be utilized with this agent, as it can cause neurologic side effects such as tremor, ataxia, and confusion, which can worsen the condition of a TBI patient (Hale & Donaldson, 1982). In a placebo-controlled trial of one patient who suffered bilateral orbito-frontal and right temporo-parietal contusions, clonidine, an alpha-adrenergic receptor agonist which reduces the firing rate of noradrenergic neurons, successfully reversed the patient's manic symptoms (Bakchine et al., 1989). Side effects to monitor include dry mouth and eyes, sedation, hypotension, and constipation. The patient case below demonstrates some of these clinical features.

A 76-year-old male falls outside his internist's office and loses consciousness. The patient is rushed to the emergency room where a head CT reveals a right-frontal-temporal-parietal hemorrhage. A craniotomy is performed to evacuate the hemorrhage, and postoperatively, the patient does well. At home a few weeks later, he becomes agitated and accuses his wife of having affairs with several men in their apartment building. His wife noted that prior to this incident he had not been sleeping well for several nights. The patient is loud, irritable, and argumentative; and his speech is difficult to interrupt. His thoughts race from one topic to another and he grandiosely proclaims to anyone who will listen, that his doctor actually hit him over the head to cause the head injury in order to rob his money. After a neuropsychiatric evaluation, the patient was treated with valproic acid, which resulted in a decrease in his irritability and agitation.

Anxiety

Anxiety refers to a state of apprehension, uneasiness, or dread that occurs in anticipation of either internal or external threats which are perceived as unpredictable or uncontrollable. The four subcategories of anxiety in the DSM-IV-TR (American Psychiatric Association, 2000) include panic disorder (PD), obsessive-compulsive

disorder (OCD), post-traumatic stress disorder (PTSD), and generalized anxiety disorder (GAD). When features of anxiety syndromes are present secondary to medical conditions such as in TBI, then anxiety secondary to medical illness is the DSM-IV-TR diagnosis to be used, as often the patient may have characteristics of several different types of anxiety syndromes present simultaneously (Hiott & Labbate, 2002). To understand the diagnostic issues involved better, each subcategory of anxiety will be described.

Panic attacks are defined as discrete periods of intense fear which develop abruptly and reach a peak within 10 minutes with the presence of at least 4 of the following 13 symptoms: palpitations, sweating, trembling, shortness of breath, the sensation of choking, chest pain, abdominal discomfort, dizziness, de-realization, chills, paresthesia, and fear of loss of control or death. To qualify for a diagnosis of PD, the patient must have recurrent panic attacks and be worried about having further episodes or be concerned about the consequences of an attack for at least one month after the initial panic attack. In some patients, the fear of having a panic attack in a situation or place from which they cannot escape creates marked discomfort and avoidant behavior known as agoraphobia (American Psychiatric Association, 2000). There are a limited number of studies where TBI and PD have been evaluated, and often this anxiety diagnosis is co-morbid with depression and alcohol dependence, as was observed by Deb and colleagues (Deb et al., 1999), who reported a 9% rate of PD in 120 patients aged 18–64 years 1 year after TBI. In several other epidemiologic studies which examined the frequency of anxiety diagnoses in patients with a TBI history, the rates of PD have been reported as 3.2%, 8.3%, and 11%, respectively, depending on whether lifetime prevalence (former) or post-TBI onset (latter two) was recorded (Silver et al., 2001; Koponen et al., 2002; Hibbard et al., 1998). Neuroanatomically the brain stem, limbic system, and prefrontal cortex have been implicated in the etiology of panic attacks (Scheutzow & Wiercisiewski, 1999).

In the DSM nomenclature (American Psychiatric Association, 2000), OCD is characterized by recurrent obsessions or compulsions that are excessive or unreasonable. Obsessions manifest as persistent impulses thoughts or images that are intrusive, inappropriate, and time-consuming, while compulsions are repetitive behaviors (checking, ordering) or mental acts (praying, counting) that the patient feels driven to perform in order to reduce the distress of the obsession. Two recent epidemiologic studies have reported rates of OCD from as low as 4.7% to as high as 14% in patients who had sustained TBI (Silver et al., 2001; Hibbard et al., 1998). Anatomically, the etiology of OCD has been linked to dysfunction of the orbital frontal cortex and subcortical circuits (Baxter et al., 1992; Grados, 2003). A study of ten patients with TBI and OCD observed that they exhibited a high frequency of obsessions which involved contamination and sexual themes as well as the need for symmetry and exactness. In addition to compulsive exercising, these patients also displayed cleaning/washing, checking and repeating compulsions. Co-morbid psychiatric diagnoses such as depression and other anxiety disorders were common, while on neuropsychological testing, these patients showed poor performance on general intelligence, attention, learning, memory, word-retrieval, and executive functions (Berthier et al., 2001).

PTSD in relation to TBI is an entity about which there has been much debate, since one of the essential criteria is that the patient who has been exposed to a threatening event must display re-experiencing symptoms, such as intrusive memories or distress when reminded about the particular trauma, recurrent dreams of the event, or the feeling that the trauma is recurring. Given that many TBI patients do not recall the event due to post-traumatic amnesia, which is a short interval after injury where the capacity to store and retrieve new information is lacking, one can argue that theoretically PTSD cannot occur in these patients. A study by Warden and colleagues reviewed 47 active-duty service members who had sustained moderate TBI with amnesia for the event. Using strict PTSD criteria, none of these patients qualified for the diagnosis, since no patient reported re-experiencing phenomena. However, when that part of the criteria was eliminated, then six patients (12.7%) received a diagnosis of PTSD (Warden et al., 1997). In a recent report of 100 patients involved in traffic accidents who sustained head injury with definite loss of consciousness, 48% reported PTSD at 3 months after the incident, and 33% suffered with this disorder one year later (Mayou et al., 2000). Some mechanisms to explain PTSD when there is a lack of recall of the traumatic event itself include: (1) recall of other distressing experiences associated with the event which occurred either before or after the period of amnesia that then serves as the "trauma"; (2) traumatic experiences may be processed by the limbic area of the brain at an implicit level outside awareness; and (3) learning of the traumatic event as told by others helps the patient to reconstruct the memory (Bryant, 2001; McNeil & Greenwood, 1996). Additional diagnostic criteria for PTSD include dissociative symptoms (de-realization, depersonalization, dissociative amnesia), marked avoidance of thoughts, feelings, or reminders of the trauma, as well as marked arousal, which can be observed as insomnia, irritability, poor concentration, hypervigilance, or a heightened startle response. To qualify for a diagnosis, these symptoms must cause impairment in functioning.

A more recently published epidemiologic study reported the rate of GAD in patients after TBI to be 1.7% (Koponen et al., 2002), but this is in contrast to other research which has noted rates in the range of 8–24% (Hibbard et al., 1998; Van Reekum et al., 1996; Fann et al., 1995). This syndrome is marked by excessive worry and anxiety about a number of issues that occur almost daily for at least 6 months. The patient is unable to control the worry and experiences at least three of six somatic symptoms which include restlessness, being easily fatigued, diminished concentration, irritability, muscle tension, or sleep disturbance. The symptoms of anxiety experienced by patients with TBI are usually attributed to the loss that patients feel in terms of their independence as well as the relation to their prior level of high functioning.

Assessment

During the evaluation of a patient with symptoms of anxiety, the neuropsychiatrist first obtains a thorough history from the patient and his family about the various situations in which apprehension is experienced, any pattern of avoidance

behavior, and accompanying physical symptoms of anxiety such as those listed above in the descriptions of anxiety disorders. As there are many medical imposters of anxiety, such as cardiac, pulmonary, and endocrinologic disorders, the neuropsychiatrist must differentiate between these diagnostic challenges. In this population of patients with TBI, seizures are a particular concern for the clinician, since the presentation of seizures can mimic anxiety syndromes. For example, during the ictus, intense fear and dread can be the sole expression of a simple partial seizure or the aura of a complex partial seizure, while OCD symptoms such as perseverative thoughts (forced thinking) can also be experienced as the aura of a seizure (Scicutella, 2001). From the standpoint of the psychiatric differential diagnosis, the clinician must consider that the patient is suffering from more than one anxiety disorder or depression. In addition, certain personality disorders may overlap with a particular type of anxiety such as borderline in PTSD or obsessive-compulsive personality disorder with OCD. In GAD and PTSD, since there is the presence of autonomic hyperarousal, the clinician must consider the possibility of the abuse of stimulants or withdrawal from alcohol and sedatives. After a careful neuropsychiatric evaluation, the physician may also need to perform laboratory tests, including a CBC, metabolic studies, an endocrinologic screen, EKG, EEG, and brain imaging if warranted, to rule out medical etiologies of anxiety (Sadock & Sadock, 2005).

Treatment

Once the neuropsychiatrist has determined the type of anxiety that the patient is suffering from, the issue of treatment must be addressed. Because no randomized placebo-controlled studies of anxiety disorders in TBI patients have been done, the general pharmacologic principles for treating anxiety disorders in patients without neurologic compromise are used, with attention to dosing regimens, side effect profiles, and drug–drug interactions. The TCAs and SSRIs have been shown to be efficacious in the treatment of the four types of anxiety disorders (Janicak et al., 1993). In case reports of patients who have suffered TBI and anxiety, the successful use of SSRIs such as sertraline in the treatment of panic attacks (Scheutzow & Wiercisiewski et al., 1999) and fluoxetine to treat OCD (Stengler-Wenzke & Muller, 2002) has been demonstrated. Venlafaxine produced almost complete remission of compulsions in one patient with OCD after an epidural hematoma (Khouzam & Donnelly, 1998); this same agent has also been shown to be effective in the treatment of GAD (Derivan et al., 1998). Side effects of these medications have been reviewed previously. Additionally, TBI patients with GAD may respond to treatment with buspirone (Buspar), a partial serotonin (1A) agonist, whose side effects include nausea, dry mouth, dizziness, and nervousness (Gualtieri, 1991). Propranolol (Inderal), a beta-blocker, which reduces adrenergic receptor activation, can also be utilized in treating patients with GAD; its adverse reactions include weakness, hypotension, nausea, and depression (Emilien & Maloteaux, 1998). The BZD class of medications, of which lorazepam (Ativan) is an example, can be useful for treating PD and GAD, but the potential

for tolerance, dependence, sedation, ataxia, memory disturbances, and occasional paradoxical disinhibition make this class less attractive for treating patients with TBI (Spier et al., 1986). MAO-I antidepressants have been of benefit in treating PTSD in patients without TBI. In addition to the potential for a hypertensive crisis as discussed earlier, more common side effects of these medications include orthostatic hypotension, edema, weight gain, insomnia, and sexual dysfunction (Sheehan et al., 1980). On occasion, antiepileptic drugs have been used to treat anxiety, but these are not first-line treatments and there are no studies using these agents in TBI patients specifically. For example, valproic acid has been used to treat PD (Woodman & Noyes, 1994), carbamazepine was successfully used to treat OCD (Koopowitz & Berk, 1997), and studies with lamotrigine (Hertzberg et al., 1999) and gabapentin (Hamner et al., 2001) have indicated some benefit in those patients suffering from PTSD. Side effects of these agents have been discussed previously. The neuropsychiatrist should also emphasize the beneficial role of psychotherapy, biofeedback, and support groups for TBI patients with anxiety in order to help them to better cope with their symptoms (Holland et al., 1999). The clinical case which follows describes some of these points.

A 70-year-old man fell off a 10-foot ladder while working at home and sustained a right temporal hemorrhagic contusion. A few months later, his family notes that he cannot stay in a closed room for any length of time. He becomes shaky, restless, and short of breath and needs to get out of the room urgently or he becomes agitated and will yell at his family. He also reports excessive worry about whether his grandchildren are safe, and he fears that they may hurt themselves. The patient is referred to the neuropsychiatrist for assessment and due to symptoms of both PD and GAD he was treated with a member of the SSRI class with marked improvement of his symptoms.

Psychosis

Psychosis is defined as the inability to distinguish reality from fantasy; or to put it another way, the psychotic patient demonstrates impaired reality testing. Clinically one can observe that patients have a thought disorder, or they may experience perceptual disturbances such as hallucinations, delusions, or paranoid ideation (Sadock & Sadock, 2005). In the DSM-IV-TR (American Psychiatric Association, 2000), psychosis is not a separate diagnostic category, but rather is a feature of a variety of other psychiatric disorders, including delirium and schizophrenia, which are particularly germane to a discussion of head trauma as will be discussed below.

Due to methodologic problems in the research of psychosis and TBI, including the type of population of patients used in studies (e.g., adults, children, open or closed head injuries) as well as the lack of standardized diagnostic criteria and variable periods of follow-up, it is difficult to assess the precise incidence and prevalence rates for psychosis and TBI (Arciniegas et al., 2003). An often-quoted study is that of Davison and Bagley, who in 1969 reviewed medical reports published between 1917 and 1960 and recorded that the rates of psychosis in these studies ranged from 0.07% to 9.8% (Davison & Bagley, 1969). Of interest are

the disparate rates of psychosis recorded in two studies where follow-up had been lengthy; in a 10–15-year study, a rate of 20% was noted and in a longer 30-year study, 1.7% was recorded (Thomsen, 1984, Koponen et al., 2002). Risk factors predictive for the development of psychosis in TBI patients include premorbid neurologic or neurodevelopmental disorders as well as having sustained a head injury before adolescence (Fujii & Ahmed, 2001). A family history of psychosis in first-degree relatives and duration of loss of consciousness were also significantly associated with psychosis post-TBI (Sachdev et al., 2001). In a recent review of 69 published case studies of psychosis after TBI, certain features emerge which appear to be typical for this phenomenon: (1) it is more commonly observed in males; (2) persecutory or paranoid delusions are the most common type of psychotic symptoms, but auditory hallucinations are also frequently observed; (3) approximately 50% of patients demonstrate symptoms before the second year after TBI, while about 75% evidence psychosis within the first four years after TBI; and (4) abnormalities as recorded by EEG were most commonly temporal slowing, whereas brain imaging demonstrated frontal lobe lesions most often, but temporal lobe lesions were also observed (Fujii & Ahmed, 2002). Cognitively, patients with TBI and psychosis demonstrate impairments on neuropsychological testing in general intelligence, verbal memory, executive function, and vocabulary (Fujii et al., 2004).

Assessment

During the assessment of the patient with psychosis, the neuropsychiatrist once again explores the recent TBI incident and the course of events during the acute hospitalization, including episodes of delirium, the latter of which is a period of acute disturbance in consciousness marked by attentional and cognitive deficits, as well as perceptual disturbances such as delusions or hallucinations (American Psychiatric Association, 2000). The patient's medical history is reviewed for other potential etiologies of psychosis such as prior head injuries, infections, vitamin deficiencies, metabolic disease, strokes, or tumors. Particularly relevant in this differential diagnosis is post-traumatic epilepsy, which is often observed as a sequelae of TBI. Moreover, a frequent complication of temporal lobe epilepsy is psychosis, which can occur prior to (aura), during (ictally), or after the seizure (postictally, either periictally or interictally) (Trimble, 1991). Medications such as steroids and anticholinergic drugs (e.g., TCAs) can cause psychotic symptoms and should be reviewed.

Psychiatric diagnoses to consider in the psychotic patient with TBI include substance or alcohol abuse/dependence, mood disorders with psychotic features, dementia with hallucinations or delusions, and personality disorders such as paranoid type. Of particular importance in this category is schizophrenia, which is defined in DSM-IV-TR (American Psychiatric Association, 2000) by a period of at least 6 months of social or occupational dysfunction in which two or more of the following symptoms are present: (1) delusions; (2) hallucinations; (3) disorganized speech; (4) disorganized behavior; (5) lack of affect and avolition. In the context

of TBI, there may be overlap with schizophrenia, since patients with the latter disorder may have sustained undocumented head injuries, or conversely, patients with schizophrenia may have cognitive deficits which make them more prone to sustain head injury. In these cases, it may be difficult to assess whether the head injury or schizophrenia is the etiology of the psychosis (Malaspina et al., 2001).

After a thorough history, the neuropsychiatrist proceeds with the physical, neurologic, cognitive, and mental status evaluation. Appropriate laboratory tests to perform include a CBC, metabolic panel, urine toxicology for substances, and when clinically indicated, EEG and brain imaging as well. If other etiologies cannot explain the patient's symptoms and it appears that the TBI is the cause of the psychosis, then the DSM-IV-TR diagnosis of psychotic disorder secondary to a general medical condition would be given.

Treatment

From a treatment standpoint, psychotic symptoms are treated with antipsychotic medications, also known as neuroleptics. As there are no randomized placebo-controlled studies of the treatment of psychotic syndromes occurring in the context of TBI, more general pharmacologic principles utilized in treating psychosis are employed. If the patient is judged to be in a state of delirium as when the patient is emerging from coma or due to another medical problem such as infection, then typical antipsychotics (dopamine receptor antagonists) such as haloperidol (Haldol) have traditionally been the drugs of choice. However, there is some controversy about using haloperidol in TBI patients due to a few reports that it negatively impacts on post-traumatic amnesia duration and cognition (Rao et al., 1985; Stanislav, 1997). Nevertheless, short-term use in delirium to improve confusion and psychosis, with appropriate tapering and discontinuation of the neuroleptic when the delirium clears, is acceptable. Side effects to be aware of include extra-pyramidal symptoms (EPS) (tremor, cogwheeling, and bradykinesia), dystonia (slow, sustained muscular contractions), akathisia (restlessness) (Sadock & Sadock, 2005), and the rarer but more serious outcome, neuroleptic malignant syndrome (NMS), which is marked by hyperthermia, rigidity, autonomic instability, and confusion (Kadyan et al., 2003). Tardive dyskinesia (TD) marked by involuntary movements of the head, limbs, and trunk can be observed as a delayed side effect of these medications usually only after years of treatment. Another concern is the fact that neuroleptics can lower the seizure threshold, making TBI patients potentially more prone to sustaining a seizure (Sadock & Sadock, 2005).

If psychosis develops at a point later in time and is unrelated to delirium, then it is advised to use atypical antipsychotics (serotonin-dopamine antagonists) which have less potential to cause EPS symptoms (Elovic et al., 2003). The common choices are risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), and clozapine (Clozaril). Beneficial use of these agents, specifically in patients suffering from psychosis after TBI, has been recorded in a few case reports (Michals et al., 1993; Schreiber et al., 1998; Butler, 2000). Side effects to monitor with these medications include orthostatic hypotension, sedation, weight gain,

hyperlipidemia, and impaired glucose tolerance. With clozapine, in particular, the increased risk of seizures and agranulocytosis make it a less attractive choice (Shaughnessy, 1995; Michals et al., 1993; Labbate & Warden, 2000). More recently there has been an association of an increased risk of stroke in patients who were treated with these medications for behavioral problems in dementia (Herrmann & Lanctot, 2005). Since patients with TBI may eventually go on to develop dementia over time, further research will be needed to guide the prescribing practice of these agents in this subset of patients. If low-potency typical antipsychotics such as chlorpromazine (Thorazine) or thioridazine (Mellaril) are utilized, EPS is less of an issue, but anticholinergic side effects are more problematic as they too can exacerbate cognitive deficits which may already be present in the traumatic brain injury population (Stanislav, 1997). A case study follows to illustrate some of these clinical points.

A 39-year-old male suffered traumatic brain injury as a result of a motor vehicle accident with brain damage in the right frontal-temporal brain regions. Subsequently, he developed delusions about being attacked by sharks and believed that he was no longer on earth but resided on Mars. These perceptions caused his attention to wander during therapy sessions and so a neuropsychiatry consult was sought. After a thorough evaluation, the patient was prescribed an atypical antipsychotic with a subsequent decrease in his delusional thinking and improvement in his ability to participate in his rehabilitation program.

Agitation

Agitation is a frequent behavioral problem associated with TBI patients and has been a source of debate in the field due to the lack of agreement about a standardized clinical definition. Since DSM-IV-TR (American Psychiatric Association, 2000) lacks a specific category for agitation, the closest approximation being personality change secondary to TBI (aggressive type), a proposal has been made to create a new diagnostic label, that of aggression, which could be subdivided into acute and chronic types. The former would be defined as lasting from a few weeks up to a few months and be essentially synonymous with delirium, while the latter would refer to the persistence of inappropriate verbal or physical behaviors beyond the two month time-frame (Silver et al., 2005). From the physiatry literature, an interdisciplinary definition has been suggested that would incorporate the elements of delirium, post-traumatic amnesia, and excesses of behavior that include some combination of aggression (verbal or physical), akathisia, disinhibition, and emotional lability (Sandel & Mysiw, 1996).

One way to help standardize the definition of agitation would be the utilization of valid and reliable scales, an example of which is the Agitated Behavior Scale (ABS) (Corrigan, 1989). This instrument includes 14 items which rate the patient's behavior in a variety of areas such as attention, impulsivity, irritability, violence, anger, wandering, pulling at tubes, and self-stimulating or self-abusing actions. Each observable behavior is rated from 1 to 4 (absent, slight, moderate, or extreme) with a cumulative score greater than 36 considered to be in the severe range of agitation. Another of these instruments is the Overt Agitation Scale (OAS), which

measures verbal aggression as well as physical aggression to self, objects, and people. Each of these four areas is rated in a range from mild to severe (Brooke et al., 1992).

The incidence of agitation has been reported to be from 35% to 96% (Levin & Grossman, 1978; Rao et al., 1985) in the acute recovery period after TBI, and from 31% to 71% in patients who were followed 1–15 years after sustaining TBI (Oddy et al., 1985; McKinlay et al., 1981). A more current study of 158 subjects in an acute-care rehabilitation setting, most of whom had severe TBI, demonstrated that approximately 50% of these patients had post-traumatic agitation as measured by the ABS; this study noted that there were no statistically significant differences as regards to gender in terms of the frequency, duration, or presentation and extent of the post-TBI agitation (Kadyan et al., 2004). In another recent study by Tateno and colleagues (Tateno et al., 2003), it was found that 33.7% of 89 patients demonstrated significant aggressive behavior when measured with the OAS 6 months after their injury. Furthermore, the aggressive behavior was significantly associated with major depression, a history of alcohol or drug abuse, frontal lobe lesions, and poorer social functioning. The enormity of this problem is emphasized in a study by Bogner and colleagues, who reported that the presence of agitation in TBI patients receiving treatment in an acute rehabilitation center, was predictive of a longer length of stay and a decrease in functional independence from a cognitive standpoint at discharge (Bogner et al., 2001). Anatomically, agitation or aggression may be explained by damage to a number of different brain areas such as the hypothalamus, amygdala, medial temporal lobe, or orbito-frontal cortex as these regions and their connections are involved in the regulation of emotion (Arciniegas & Beresford, 2001).

Assessment

In acute agitation, the neuropsychiatrist must first assess if there are other underlying medical conditions (in addition to TBI) such as infections, metabolic imbalances, or medications such as narcotics, anticholinergic agents, or steroids which can be contributing to the patient's delirium. To treat the symptoms of acute agitation, neuroleptics such as haloperidol are used. Droperidol (Inapsine), an antipsychotic agent similar to halperidol, was recently reported to be effective in treating acute agitation in 27 patients with TBI (Stanislav & Childs, 2000). Other medications sometimes used in the acute setting include the BZDs such as lorazepam (Mysiw & Sandel, 1997). In a recent report of 11 TBI patients who were between 4 and 23 days post-injury, the treatment for acute agitation was the combined use of amantadine, methylphenidate, and trazodone. All the patients were noted to have resolution of their agitation as well as improvement in their cognitive function (Rosati, 2002). Additional randomized, controlled prospective studies are needed to determine the efficacy of this treatment approach.

The neuropsychiatrist who is asked to evaluate a patient with the chronic form of agitation in his/her office will need to take a thorough history and perform a complete neuropsychiatric examination as well as any necessary laboratory studies

in order to be able to rule out other medical problems which may be the underlying etiology for the agitation. Included in the possible diagnoses would be a new episode of delirium, being post-ictal, pain syndromes, and the use of alcohol or illicit drugs. Psychiatric diagnoses in which aggression can be seen include major depression, bipolar disorder, anxiety disorders such as PTSD and GAD, and personality disorders such as antisocial type (Silver et al., 2005).

Treatment

There are few pharmacological agents with prospective studies of a randomized, placebo-controlled design which can definitively guide the treatment of agitation in TBI patients, but the beta-blocker propranolol and the stimulant methylphenidate have been exceptions in this regard. In separate studies of propranolol, it has been shown that there is either a statistically significant reduction in the maximum intensity of the episodes of agitation (Brooke et al., 1992) or in the actual number of aggressive episodes which occur (Greendyke et al., 1986). Stimulants such as methylphenidate have been used successfully to treat temper outbursts marked by belligerence and hostility in 38 male patients who had sustained TBI 2 years prior to the study (Mooney & Haas, 1993). Amantadine, a dopaminergic agent, has been demonstrated to be of benefit in the treatment of aggressive behavior in TBI patients as noted in case reports (Chandler et al., 1988) as well as in a retrospective case analysis (Nickels et al., 1994). The anticonvulsants including carbamazepine (Kennedy et al., 2001; Azouvi et al., 1999; Chatham-Showalter, 1996), valproic acid (Wroblewski et al., 1997), gabapentin (Rybach & Rybach, 1995), and lamotrigine (Pachet et al., 2003) provide another option in the treatment of TBI patients with agitation, as has also been reported in case reports and open-label trials. Antidepressants, such as sertraline in the SSRI class (Kant et al., 1998), amitriptyline in the TCA group (Mysiw et al., 1988), trazodone (Rowland et al., 1992), and bupropion (Teng et al., 2001) have been noted to be useful in treating agitation and aggression in this population as well. Buspirone, in the anxiolytic class, has been observed to be effective in the treatment of angry outbursts and behavioral problems in TBI patients (Gualtieri, 1991; Holzer, 1998). The side effects of all these medications have been previously reviewed. Although other agents such as the mood stabilizer lithium (Glenn et al., 1989) or the benzodiazepines (Freinhar & Alvarez, 1986) have been used in the management of agitation, these medications are probably best avoided in the TBI population due to the potential neurotoxic effects (tremor, delirium, and seizures) of the former agent and possible cognitive disturbances (attention, alertness and memory) of the latter (Perna, 2004). The use of ECT as an alternative treatment to medication was found to help one patient with severe TBI and behavioral disturbance when he proved unresponsive to a variety of psychopharmacologic agents (Kant et al., 1995).

Finally, the neuropsychiatrist should also work in conjunction with the therapists on the rehabilitation team in order to be aware of the behavioral approaches which are being utilized to help the patient deal with agitation and aggression (Rothwell et al., 1999). These can include altering the environment to decrease provocative

stressors, coping skills training, and behavior modification involving reinforcements for appropriate behavior (Watson et al., 2001). The family members should also be encouraged to seek supportive psychotherapy to help them cope with the injured loved one's behavioral disturbance and personality changes. A patient case can highlight some of these points.

A 70-year-old woman sustained head trauma when her car was broadsided by a truck. She sustained a left hemispheric subarachnoid hemorrhage with extension into the bilateral sylvian fissures as well as a left parietal/occipital subdural hematoma. Several months later when the patient was at the subacute rehabilitation facility, she became very angry when she felt that the staff did not appreciate that her abilities to perform tasks were much better than the rest of the patients there. She believed that she did not belong in the facility and was often packing her bags and threatening to leave the building. On one occasion, she ran out of the therapist's office into the parking lot with the staff in pursuit, and in another incident, while on a weekend pass to visit family, she refused to get in her daughter's car to be driven back to the rehabilitation center. She was physically aggressive towards family members, including biting, kicking, and hitting them. After evaluation with the neuropsychiatrist, valproic acid was used to treat the patient and she demonstrated a dramatic improvement in behavioral dyscontrol.

Arousal and Attention

When a patient sustains TBI, the physiologic state known as arousal, which is defined by the level of wakefulness and the intensity of stimulation needed to elicit a meaningful response by the individual, can be altered by varying degrees. Whereas in normal consciousness, the person is fully awake and able to respond cognitively and emotionally to both internal needs as well as to external stimuli, the drowsy patient sustains wakefulness only with the application of some form of external stimuli. These patients are often inattentive and confused. At the level of stupor, a patient can only be roused by vigorously repeated and often noxious stimuli; once the stimulus ceases the patient lapses back into unresponsiveness. The comatose patient appears to be asleep and incapable of being aroused by either external stimuli or their own internal needs, while the patient in a vegetative state undergoes alternate sleep–wake cycles, but doesn't regain awareness or purposeful behavior. When this condition extends beyond 1 month, the term *persistent vegetative state* is applied (Adams et al., 1997; Mesulam, 2000).

Overlapping with this concept is that of attention, since the ability to attend or concentrate on stimuli is predicated on one's degree of arousal. Impaired attention is a problem frequently observed in patients who have suffered TBI and its impact upon rehabilitation efforts is profound, since other cognitive processes such as encoding and storing items in memory, problem-solving, and language skills are dependent upon one's ability to focus on various stimuli (Stierwalt & Murray, 2002). The construct of attention is further divided into: (1) basic attention or the capacity to orient to simple stimuli; (2) selective attention, or the ability to prioritize some stimuli over others; (3) sustained attention, or vigilance, which represents

the capacity to maintain attentional focus over time; and (4) divided attention, in which one must respond to or process multiple stimuli simultaneously (Niemann et al., 1996). Often after TBI, the basic attention abilities recover, but psychometric testing in a few recent studies reveal that TBI patients, several years post-injury, still struggle with cognitively challenging tasks when impairments in divided and sustained attention persisted (Stierwalt & Murray, 2002; Mangels et al., 2002; Dockree et al., 2004; Vanderploeg et al., 2005).

Anatomically, the arousal and attentional systems are complex and widely distributed through the brain and involve the ascending reticular formation of the brain stem, which extends from the medulla to the midbrain: the hypothalamus, thalamus, basal forebrain, limbic system, anterior cingulate, and parietal, temporal, and prefrontal cortical areas. Damage to any of these regions via mechanical injury or diffuse axonal impairment can disrupt the various neurotransmitter pathways (noradrenergic, dopaminergic, and cholinergic) which play key roles in the modulation of arousal and attention (Mesulam, 2000). Evidence for the latter neurotransmitter's role in this cognitive domain was highlighted in a recent study of TBI patients whose neuropsychological profile demonstrated decreases in sustained attention and reaction times while the morphometric analysis of their brain imaging revealed reduced gray matter density in the regions of all the major cholinergic pathways (Salmond et al., 2005).

Assessment

The neuropsychiatrist who evaluates the patient with arousal and attention deficits needs to conduct a thorough history with regard to factors which can induce a decreased level of awareness, such as infections, metabolic abnormalities, seizures, strokes, drug intoxication, and medications (Adams et al., 1997). A careful neurologic examination will include testing cranial nerves for pupillary reactivity, ocular motor movements, and oculovestibular reflexes to gauge brain stem function. Additionally, the level of arousal is assessed via the patient's ability to respond verbally, motorically, or via eye opening to various stimuli. Then, depending upon the patient's degree of alertness and ability to participate, a bedside cognitive evaluation which highlights tests of attention should be performed. Some examples of these tests include the digit-span (repetition of a list of numbers in which 7 ± 2 digits forward and 5 ± 1 digit in reverse is normal); a continuous performance test (the patient lifts his/her arm whenever the letter "A" is read aloud amongst a group of letters); trail-making tests (the patient connects in proper sequence an array of numbers or alternating numbers and letters which are arranged haphazardly on a paper); and an alternating sequences task (the patient must imitate a series of three hand gestures—palm, fist, edge of hand—repetitively without error). These tests help to determine if there are attentional deficits as manifested by distractibility, perserveration, or response inhibition (Mesulam, 2000). For more extensive cognitive evaluation, a neuropsychological battery should be ordered which can further assess the subsets of attention with more sophisticated measures, sometimes using computerized auditory or visual stimuli (Stierwalt & Murray, 2002; Cicerone,

2002). An alternative approach to assessing attention that can be helpful in an acute rehabilitation setting, is the use of a rating scale based on the staff's observations of patients in everyday activities. As has been discussed, a patient may have deficits in various subtypes of attention and thus performance on different tasks may help to categorize what these impairments might be. Examples of these include the neurobehavioral rating scale (NRS) (Levin et al., 1987), which documents alertness, attention, and fatigability, while the Moss Attention Rating Scale includes items for arousal, alertness, sustained attention, distractibility, and divided attention (Whyte et al., 2003). Laboratory workup to elucidate the etiology of a diminished level of arousal should include routine blood tests, urinalysis, toxicology, brain imaging, lumbar puncture if warranted, and an EEG, as an alteration in brain waves occurs in virtually all disturbances of consciousness (Adams et al., 1997).

Treatment

Increasing a patient's level of arousal and attention after TBI has been attempted with medications as well as through nonpharmacologic means. An example of the latter is the study by Wilson and colleagues (Wilson et al., 1996), who provided environmental sensory enhancement to 24 patients in a vegetative state. A more robust response, as measured by frequency of eye-opening and body movements, was noted when each of the five senses was stimulated at each treatment session, as compared to when just a single sense was stimulated. In addition, an increased level of arousal was also observed when the individual was exposed to personal favorite stimuli such as foods, songs, or photos as contrasted with the use of neutral stimuli. To improve attention, nonpharmacologic approaches that have been utilized include teaching compensatory strategies, such as reducing distracting elements in the environment and taking breaks to maximize one's performance (Mateer et al., 1999), as well as learning to anticipate task demands, to repeat information, and to get clarification when having to manage tasks in the setting of time constraints (Cicerone, 2002).

In the pharmacologic treatment of patients with deficits in arousal and attention, one approach that has been used is based on the idea of enhancing neurotransmitter systems which have been disrupted secondary to TBI. As discussed previously, psychostimulants such as methylphenidate and dextroamphetamine serve to augment the concentration of dopamine and norepinephrine by increasing their release and blocking their reuptake in the synapse. Controlled studies have been conducted with both of these agents (Plenger et al., 1996; Evans et al., 1987), but the most frequently documented positive effect in neuropsychologic tests of attention was in processing speed (Whyte et al., 1997), while the benefit of these medications to increase attention or reduce distractibility has been less certain (Whyte et al., 2002, 2004). Case studies of TBI patients, including individuals in the persistent vegetative state or minimally conscious state, have indicated that amantadine, another dopaminergic agent, improves attention, concentration, and arousal (Nickels et al., 1994; Kraus & Maki, 1997; Zafonte et al., 1998). Other dopaminergic agents which have been shown to be useful in enhancing alertness include levodopa and

bromocriptine (Lal et al., 1988; Powell et al., 1996). Modafinil, which appears to activate limbic areas and is approved for narcoplepsy, is an obvious potential choice for treating underarousal in TBI (Teitelman, 2001; Elovic, 2000). Antidepressants with noradrenergic effects such as amitriptyline and desipramine have also been demonstrated to improve arousal and responsiveness in three patients with severe TBI (Reinhard et al., 1996). The side effects of these medications have been reviewed in previous sections.

Since TBI often results in the dysfunction of the cholinergic system in the hippocampus and frontal cortical areas, regions which play a pivotal role in the cognitive function of attention (Salmond et al., 2005; Arciniegas et al., 1999), the use of AchE-Is may also be useful pharmacologic agents in treating these deficits, as several studies have indicated (Griffin et al., 2003; Kaye, 2003; Zhang et al., 2004). Side effects of these medications have already been reviewed. It is noteworthy that there is an overlap in both the neuroanatomic structures and the neurotransmitter systems which play key roles in the biology of arousal and attention, as well as motivation, since the latter provides an individual with the drive to respond to stimuli once he is alert and able to concentrate. Therefore the use of similar pharmacologic agents to treat disorders of these functions appears to be a sound clinical approach. A case vignette highlights the issues involved in patients with problems of arousal and amotivation.

A 34-year-old male with a history of cardiomyopathy suffered a cardiac arrest with a prolonged period of unresponsiveness of unknown duration. He was resuscitated and placed on life support and subsequently underwent successful cardiac transplantation. After recovery from his surgery, he was noted to be fatigued and sleepy a lot of the time. He would close his eyes during rehabilitation sessions and say, "I want to sleep," in a monotone voice. Left to his own devices, he would immediately return to his room to sleep. He needed a great deal of repeated external stimulation by his therapists to enable him to remain alert and concentrate on a task for even brief periods. In addition, due to the anoxic encephalopathy which he suffered as a result of the cardiac arrest, his short-term memory was poor, and he lacked drive to do things spontaneously. The patient was treated with a variety of stimulants, including methylphenidate, with only slight improvement. Subsequently, the patient was placed on high-dose venlafaxine, as his clinicians thought his symptoms were consistent with depression; and on this medication, he did show some improvement. Later in his course of treatment, donepezil and modafinil were added sequentially to help increase his level of attention. Therapists in the rehabilitation center who work with him have noted an improved level of alertness and ability to concentrate as well as increased spontaneity in answering questions with this combination of pharmacologic medications.

Dementia

The cardinal feature of dementia as defined by DSM-IV-TR (American Psychiatric Association, 2000) is a deficit in memory. In addition, there must be a decline in at least one other cognitive sphere such as aphasia (disorder of language), apraxia (inability to perform a previously learned motor activity such as teeth brushing,

despite having intact motor and sensory abilities), agnosia (impaired recognition of visual, auditory, or tactile stimuli which cannot be attributed to sensory loss, language disturbance or global cognitive deficits), or finally executive function (organizing, planning, sequencing skills). Furthermore, these deficits impact on social or occupational functioning and represent a significant decline from the person's baseline. In the acute period just after TBI, cognitive deficits can be present secondary to delirium or post-traumatic amnesia. Dementia is a more insidious process and refers to residual deficits which persist for months or years post-TBI. The prevalence of dementia after TBI is not precisely known but has been reported to occur at a rate of between 5% and 17.5% (Koponen et al., 2002; Gualtieri & Cox, 1991), whereas the prevalence of memory disturbances alone, the most common cognitive problem after TBI, ranges from 23–79% (Levin, 1990). Dementia in TBI patients may be due to damage of the frontal anterior and medial- temporal cortices as well as the underlying white matter which connects cortical to subcortical areas (Arciniegas & Beresford, 2001). In addition, since acetylcholine-rich hippocampal regions which are responsible for short-term memory function are frequently damaged in TBI, cholinergic dysfunction is believed to be etiologically related to the memory impairment seen in these patients (Arciniegas et al., 1999). Whether TBI is a definite risk factor for Alzheimer's disease (AD) remains controversial, as some research has shown an increased risk for AD in patients with head injury and other studies have not (Plassman et al., 2000; Williams et al., 1991; Mehta et al., 1999). One possible mechanism to explain the neuropathological overlap in these two entities suggests that the presence of the apo-lipoprotein E (epsilon) 4 allele which retards neural repair after trauma, serves in turn as a risk factor for the deposition of beta-amyloid protein and the subsequent formation of neurodegenerative plaques in AD (Koponen et al., 2004; Jellinger, 2004; Luukinen et al., 2005). In an epidemiologic study of TBI patients, it was found that the observed time from the brain injury incident to the development of AD was less than expected (Nemetz et al., 1999), implying that TBI may hasten the yet undetermined cascade of events necessary to precipitate AD in those patients who are ultimately predisposed to its development. This study gives support to the Satz model of cognitive reserve, which hypothesizes that the brain capacity which is available to carry on the basic ability to function as a human being differs for each person. Therefore dementia would occur at the point where there is a critical reduction in those neurons necessary to carry on these basic functions; this decrease in neurons could be due to normal aging, disease, or external factors such as toxins or TBI (Satz, 1993).

Assessment

The evaluation of a patient with cognitive decline begins with a thorough history about the current TBI incident and its subsequent treatment as well as a review of medical and surgical problems including whether there have been prior TBIs, falls, seizures, or strokes. Additionally, the patient's psychiatric history, family history of neurologic and psychiatric problems, medications, and social history, including level of education, alcohol and drug use, and driving issues should also

be assessed. Questions about the impact of the cognitive deficits on the patient's ability to function safely and independently at home, socially, or in the workplace if applicable are key points to address. A comprehensive physical and neurologic examination, as well as a cognitive assessment which tests for attention, memory, and frontal lobe functions, is vital, as is a thorough mental status exam which assesses for psychiatric symptoms. Laboratory tests include a CBC, electrolytes, liver function tests, B12 and folate, as well as brain imaging such as an MRI (magnetic resonance imaging). Neuropsychological testing can help to establish the patient's baseline in terms of current cognitive strengths and weaknesses. The neuropsychiatrist must perform a thorough evaluation to rule out other possible etiologies in the differential diagnosis of cognitive decline, such as hydrocephalus, strokes, neoplasm, subdural hematoma, vitamin deficiencies, delirium, depression, and endocrine abnormalities such as hypothyroidism (Small et al., 1997; Frederiks et al., 2002) as well as hypopituitism, which has been reported in TBI patients with cognitive impairment (Popovic et al., 2005; Springer & Chollet, 2001).

Treatment

An important issue to address in treating TBI patients who have cognitive deficits is whether a concomitant diagnosis of depression is present. In a recent study, 28.4% of 74 patients with mild or moderate TBI who also suffered from major depression were found to have significantly lowered scores on measures of working and verbal memory, processing speed, and executive function as compared to patients without this diagnosis (Rapoport et al., 2005). In another study of 15 patients with mild TBI and depression, neuropsychological tests were noted to improve when their mood symptoms had been successfully treated with the antidepressant sertraline (Fann et al., 2001). Since TBI may produce cognitive impairment neurochemically via the disruption of cholinergic function, it has been suggested that using cholinergic-enhancing medications such as choline precursors or AchE-Is may be an appropriate pharmacologic approach. Cytidine 5′diphosphocholi is a choline precursor which has been reported to be effective in improving cognition after TBI in both case studies (Spiers & Hochanadel, 1999; Leon-Carrion et al., 2000) as well as in a randomized double-blind placebo-controlled study of fourteen patients (Levin, 1991). Although physostigmine, an AchE-I, has not been shown to be consistently effective in the treatment of memory deficits of TBI patients in several different studies (Goldberg et al., 1982; Levin et al., 1986), donepezil, another member of the AchE-I class, has been reported to improve memory in TBI patients in open-label and case study reports (Taverni et al., 1998; Whitlock, 1999; Whelan et al., 2000; Masanic et al., 2001; Morey et al., 2003). More recently in a 24-week randomized, placebo-controlled, double-blind, cross-over trial with 18 patients who had sustained TBI less than 6 months prior to the study, Zhang and colleagues documented that donepezil significantly increased neuropsychological testing scores in short-term memory and sustained attention (Zhang et al., 2004). In a non-randomized, open-label study of 111 outpatients with TBI who either received donepezil or one of the two newer AchE-Is, namely, rivastigmine

(Exelon) or galantamine (Reminyl), the areas of vigilance, concentration, initiation and general function were noted to be subjectively markedly improved in 61% and modestly improved in 39% of this population (Tenovuo, 2005). Furthermore, AchE-Is have also been shown to benefit mood, affect, and social interaction in brain-injured patients (Kaye, 2003; Whelan et al., 2000). Large-scale randomized, double-blind placebo controlled studies are needed to clarify the benefits of these agents in TBI patients. A patient case provides an example of this clinical problem.

A 50-year-old male sustained a left frontal temporal brain injury 3 years ago. Despite cognitive remediation and the use of compensatory strategies such as a memory book in which he writes his daily activities, his memory is still poor. He has trouble organizing what tasks he must complete and requires a lot of supervision from his wife. Due to his cognitive deficits, he was unable to return to his occupation as a clerk in an insurance company. After neuropsychiatric assessment, the patient decided to be started on donepezil with modest improvement in his memory.

Sexual Dysfunction

After TBI, a patient's sexuality can be altered in a variety of ways and he or she can experience difficulties not only with libido and the physical sexual act, but also develop problems with self-esteem and relationship skills. The clinical categorization of the various subtypes of sexual dysfunction as per DSM-IV-TR (American Psychiatric Association, 2000) nosology is beyond the scope of this chapter. For the purposes of this discussion, the focus of the sexual problems reviewed will be those commonly observed in relation to TBI; hence the appropriate diagnostic label would be sexual dysfunction secondary to TBI. In TBI patients, the rate of sexual dysfunction has been reported to be in the range of 4–71% (Sandel et al., 1996). While most often patients suffer from hyposexuality as a result of the brain injury, hypersexuality can also occur as was noted in 14% of subjects in one study (Kreutzer & Zasler, 1989). Of note, in a small minority of men with TBI, sexually aberrant behaviors such as inappropriate touching, exhibitionism, or overt sexual aggression has also been reported (Simpson et al., 1999). Neuroanatomically, hyposexuality has been related to lesions of the medial orbital gyrus of the frontal lobe, hippocampus, anterior thalamus, and hypothalamus (Elliott & Biever, 1996), while hypersexuality can occur with damage to the frontal lobe and bilateral temporal lobes (Zencius et al., 1990, Wesolowski et al., 1993). A clinical example of a sexual problem in this population of patients can serve to illustrate some key issues.

A 40-year-old male suffered traumatic brain injury after a motor vehicle accident which caused injury to the right frontal-temporal brain regions. Subsequent to this he was observed exposing himself and making inappropriate sexual overtures to female staff as well as family members. He began to masturbate in public places while using pornographic materials. His behavior is disruptive to his rehabilitation efforts and he is referred to the neuropsychiatrist for evaluation.

Assessment

As with other neuropsychiatric conditions, obtaining a history to try to narrow down the diagnostic possibilities is key, as sexual dysfunction after neurologic insults can be due to either genital and/or nongenital causes. The patient and his/her sexual partner should be asked about the patient's premorbid and post-TBI sexual history, including marital status, sexual preference, sexual activities, sexual abuse, quality of relationships, libido, arousal, and physiologic function (erection, ejaculation, vaginal lubrication, orgasm). Any sexually intrusive behaviors—which can range from inappropriate remarks to aggressive behavior, including rape—should also be explored in the TBI patient (Bezeau et al., 2004). Since many medications have sexual side effects and because diseases such as diabetes or sexually transmitted diseases can cause sexual dysfunction, inquiry into these topics is pertinent. Endocrinologic function is also particularly relevant since brain injuries which affect the pituitary gland, and hence hormonal levels, could be responsible for a patient's sexual problems. Decreased sensation or hypersensitivity, decreased mobility secondary to paralysis or orthopedic injuries, as well as tremor or balance problems, are all obvious impediments to sexually pleasurable activity and must be addressed as well. Prior psychiatric illness is relevant, as decreased or increased libido can be observed within the constellation of mood and anxiety disorders (Zasler & Martelli, 2005). A history of seizures is important to inquire about as epilepsy is a common sequelae of TBI (about 12% in severe TBI) (Annegers et al., 1980), and those with temporal lobe epilepsy often suffer with hyposexuality. Since cognitive-behavioral and emotional problems can limit one's ability to effectively maintain an intimate relationship, it is important in the examination of the TBI patient to explore the impact of relevant issues such as poor concentration, memory deficits, motivation, lack of confidence, excessive dependency and loss of equality in the relationship, disinhibition, and insensitivity to a partner's needs. As part of the neuropsychiatrist's role, he/she can order lab tests such as hormone levels (follicle-stimulating hormore [FSH], leutinizing hormone [LH], estrogen, testosterone) and then target appropriate ancillary consultations to the physiatrist, endocrinologist, gynecologist, or urologist (see the chapter on neurourology) to address those sexual issues which do not appear to be under his/her purview (Zasler & Martelli, 2005; Oddy, 2001).

Treatment

If the nature of the problem is ultimately determined to lie in the neuropsychiatric domain, the professional in this field can utilize different approaches to help the patient and his/her partner. In the above clinical case where hypersexuality is the clinical problem, one form of treatment would be to take advantage of the sexual side effects of antidepressants such as the SSRIs, which are known to decrease libido and cause problems in achieving ejaculation, orgasm, and erections (Krueger & Kaplan, 2002). Sometimes, mood stabilizers, especially anticonvulsants, are used to treat hypersexuality if this symptom is viewed as part of a

manic or hypomanic state. If these fail, then sexual desire can be diminished with anti-androgens such as medroxyprogesterone (Britton, 1998) or depot-leuprolide acetate (Lupron) (Krueger & Kaplan, 2002) as was successfully done in the above-described clinical scenario. These medications are gonadotropin-releasing hormone analogs which cause a reduction in the pituitary production of LH and FSH, which in turn leads to a decrease in testosterone. Prior to starting this treatment, the patient requires baseline hormonal levels and a bone density evaluation, as bone loss can be a side effect of these agents (Krueger & Kaplan, 2002). A behavioral plan focused on modification of these inappropriate actions should also be undertaken as part of the treatment.

Hyposexuality is a more common sexual dysfunction problem. Antidepressants, antipsychotics, anticonvulsants, but also antihypertensives, stimulant medications, and anticholinergics can be the source of decreased libido; therefore, dosage modification or elimination of the medication entirely may help to improve a patient's sexual interest and performance (Aloni & Katz, 1999). Conversely, the neuropsychiatrist must also assess whether depression is the underlying cause of the sexual dysfunction, in which case appropriate treatment may improve the patient's desire. Utilizing medications which do not have sexual side effects, such as bupropion or nefazadone (Serzone), an inhibitor of serotonin and norepinephrine reuptake in the synapse whose primary adverse effect is sedation, may be more beneficial in this scenario (Hirschfeld, 1999). Psychotherapy, which can include both individual and couple's counseling to help the patient and his partner deal with the practical issues of sexual relations as well as emotional issues, should be part of the treatment paradigm. Since the reported rates of marital breakup after TBI are high, the role of psychotherapy in this area must be underscored. With a TBI group therapy format, patients can practice social skills with peers and have the opportunity to discuss common sexual problems and how to cope with them (Katz & Aloni, 1999), while the availability of sexuality handbooks which address these topics can also be valuable resources for TBI patients who have sufficient cognitive abilities to benefit from this approach (Simpson & Long, 2004). Finally, in those cases of TBI patients with sexually intrusive behaviors, behavioral programs which focus on establishing clear boundaries in relationships, encourage adaptive and appropriate behaviors, and provide a relapse prevention plan have been demonstrated to be successful (Bezeau et al., 2004).

Conclusion

As has been observed from the patient vignettes in this chapter, the neuropsychiatric complications of TBI are numerous and complex. In reviewing our progress along the neuropsychiatric historical timeline, it is observed that we have advanced from the point where there was merely a glimmer of understanding about the possible existence of a relationship between brain and behavior, to our more sophisticated, modern ideas about the brain and its definitive roles in emotion and cognition. Yet despite learning about brain–behavior connections through the deficits suffered by

TBI patients, much research still needs to be done to understand the intricate nature of these neuronal ties, as well as to improve the outcomes of our patients who have suffered these injuries. There is debate in the literature about whether cognitive and psychiatric sequelae of TBI are the result of specific brain lesions, psychologic reactions to trauma, pre-morbid psychiatric illness [as was proposed in a study which noted an increased relative risk of 1.6 for subsequent TBI in patients who had had any indicator of psychiatric illness in the year prior to TBI (Fann et al., 2002)], or a combination thereof. For this reason, future studies of patients should be prospective in design using standardized diagnostic criteria which will more accurately categorize both the degrees of TBI (mild, moderate, severe) as well as the specific psychiatric syndrome. This will help to better predict outcomes of psychiatric co-morbidity, cognitive impairment and functional status, as well as to allocate resources appropriately to assist these patients in repairing their lives. In addition, randomized, blinded, placebo-control studies of psychopharmacologic agents are crucial to providing a rational, consistent approach to treating the various neuropsychiatric consequences of TBI. With these improvements as a start, patients who have had the misfortune of sustaining TBI can have the hope of enjoying an improved quality of life.

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