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# Identifying and Managing Agitated Behaviors Following Traumatic Brain Injury

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## Clinical Vignette

*JD is a 24-year-old, right-hand dominant female who incurred traumatic injuries from a bicycle accident. She was traveling approximately 25 mph when she lost control of her bicycle and flew forward over the handlebars, rolling several times. JD was helmeted and sustained a brief loss of consciousness at the scene. En route to the hospital, she was intubated for altered mental status and combativeness. A head CT demonstrated subarachnoid hemorrhage in the interpeduncular cistern and small areas of acute intraparenchymal hemorrhage, the largest measuring 6 mm in diameter in the right frontal region. MRI of the brain five days after her injury was consistent with diffuse axonal injury and demonstrated several areas of gradient blooming along both sides of the corpus callosum, parenchymal hemorrhage within the left basal ganglia, and small foci of contusions involving the left temporal lobe and right frontal lobe (Figure 1). Additionally, she was found to have a mildly displaced fracture of the right distal radius.*

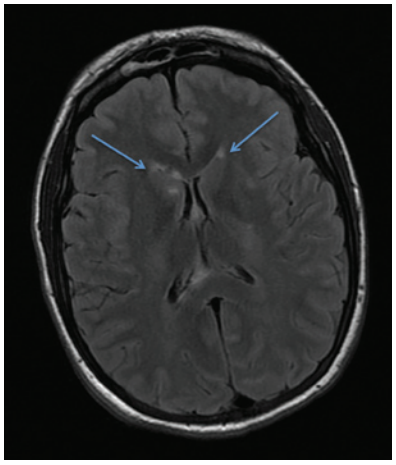

FIGURE 1: **Axial T2 Flair**
Hyperintense areas noted within the genu of the corpus callosum and right caudate.

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Doctors Reddy, Hong, and Huie have reported no relationships with proprietary entities producing health care goods or services.

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*Once medically stable, JD was transferred to the Inpatient Brain Injury Program at the UPMC Rehabilitation Institute at UPMC Mercy.*

*Early in her rehabilitative course, JD demonstrated significant restlessness. She would impulsively attempt to get out of bed, and was observed to have poor sleep initiation with fragmented sleep at night. JD became agitated and fatigued following visits from multiple family members and friends. She was physically aggressive and easily distracted during her therapies. She was unable to adhere to her right upper extremity weight-bearing precautions, and perseverated on the discomfort. On two occasions, she destroyed her right wrist splint, and new splints were reapplied. Vital signs showed a consistent tachycardia and mild hypertension without any fever or evidence of infection. Further management by the brain injury team was then instituted to address these problems.*

## Epidemiology

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. In the United States, 1.7 million TBIs occur annually, resulting in 52,000 deaths and 275,000 hospitalizations.[1] The leading causes of civilian TBI include falls (35.2%), motor vehicle accidents (17.3%), incidents in which a person is unintentionally struck by or against another person or object (16.5%), and assaults (10%).[1] It is estimated that long-term disability occurs in 43% of TBI survivors requiring hospitalization.[2] The economic burden has been estimated to be $76.3 billion, with fatalities and hospitalization accounting for 90% of the cost.[3]

TBI is commonly associated with neurobehavioral problems that include irritability, depression, disinhibition, agitation, aggression, nighttime disturbances, delusions, euphoria, hallucinations, and anxiety.[4] Posttraumatic agitation is one of the more frequent and challenging sequelae of brain injury, and agitated patients may be disruptive in therapies, demonstrating poor participation in their own recovery. A study of 69 patients with TBI showed that agitated behavior was inversely associated with engagement in rehabilitation therapy, even after controlling for injury severity.[5] Agitated patients may be unsafe and pose a physical threat to staff, patients, and family. They frequently require more supervision from rehabilitation staff and make greater demands upon resources. A longitudinal study of 340 consecutive patients admitted to an acute TBI rehabilitation unit demonstrated that the presence of posttraumatic agitation was associated with longer rehabilitation length of stay, a decreased rate of discharge to private residence, and decreased cognitive FIM scores at discharge.[6]

## Definition of the Problem

The reported frequency of posttraumatic agitation differs between studies because a clear consensus definition is lacking. In a survey of the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation, there was a wide variation in how physiatrists rated the defining characteristics of agitation.[7] In this study, physical aggression, explosive anger, increased psychomotor activity, impulsivity, verbal aggression, disorganized thinking, perceptual disturbances, and reduced ability to maintain or appropriately shift attention were rated by at least 50% of the 129 respondents as very important or essential to agitation. Lombard and Zafonte have defined agitation as "verbal or physical aggression during posttraumatic amnesia that occurs in the absence of other physical, medical, or psychiatric causes, identified by a score of 22 or higher on the Agitated Behavior Scale."[8]

A prospective study of 100 inpatient rehabilitation patients using a strict definition of agitation found 11% of patients experienced agitation while 35% exhibited restlessness.[9] This study defined agitation as episodic motor or verbal behavior that interfered with patient care or required physical or chemical restraints to prevent damage to persons or property. In eight of the 11 subjects with agitation, the symptoms lasted less than one week. In contrast, a retrospective review of 80 inpatient rehabilitation TBI patients in Australia found that 70% of patients demonstrated agitation for an average of 32 days during rehabilitation.[10]

TABLE 1:

**Rancho Los Amigos Levels of Cognitive Functioning**

| | |
|---|---|
| Level I | No Response |
| Level II | Generalized Response |
| Level III | Localized Response |
| Level IV | Confused-Agitated |
| Level V | Confused-Inappropriate |
| Level VI | Confused-Appropriate |
| Level VII | Automatic-Appropriate |
| Level VIII | Purposeful-Appropriate |

In a prospective study examining gender differences in a cohort of 158 patients, posttraumatic agitation was seen in approximately 50% of patients after TBI, with symptoms lasting typically less than 10 days.[11] There were no significant gender differences in the frequency, duration, presentation, or extent of posttraumatic agitation.

Agitation is a characteristic of the fourth stage of recovery in the Rancho Los Amigos Scale of Cognitive Functioning (Table 1).[12] During this stage, patients demonstrate posttraumatic amnesia (PTA), a state of anterograde amnesia marked by confusion, impaired orientation, and inattention. Cognitive difficulties associated with PTA are thought to contribute to agitation, because patients may react out of proportion to external stimuli. A descriptive study of eight TBI patients monitored daily over 28 days with the Agitated Behavior Scale (ABS) revealed that improved cognition was associated with resolving agitated behavior, and minimal agitated behavior was observed in those who emerged from PTA.[13]

Of particular importance in defining agitation is clearly distinguishing it from akathisia, which also can result from TBI. Akathisia, a syndrome of inner motor restlessness, often can be confused with agitation. Akathisia can be caused by TBI, but the pathophysiology is not well understood. Signs of akathisia include pacing, rocking to and fro, fidgeting, repetitive actions, and an inability to sit or stay still. It is important to differentiate akathisia from agitation, because akathisia is often a side effect of medications such as antipsychotics, antiemetics with antidopaminergic properties, selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium, buspirone, and calcium channel blockers. Akathisia is thought to be primarily from excessive type 2 dopamine receptor antagonism, but other neurotransmitters, such as histaminergic, cholinergic, and adrenergic systems, may be involved.[14]

## Pathophysiology

The pathophysiology of TBI is a complex, heterogenous process consisting of primary injury and secondary injury. *Primary injury* is the damage that occurs at the moment of impact, and can result from a variety of mechanisms that include direct impact, rapid acceleration and deceleration, penetration, and blast waves. These mechanisms may result in focal injuries or more diffuse damage from shear of cerebral axons. *Secondary injury* is a complex biochemical cascade that occurs in response to the initial primary injury. Secondary injury in TBI likely results from excitotoxic mechanisms that lead to elevated levels of excitatory neurotransmitters.

Diffuse brain injuries may result in vascular injury, cerebral edema, hypoxic-ischemic injury, and more commonly, diffuse axonal injury (DAI). Diffuse axonal injury typically results from rapid acceleration and deceleration forces upon the brain causing shearing of communicating axons at the gray and white matter junction of predominantly midline structures, such as the corpus callosum, internal capsule, superior cerebellar peduncle, and brainstem. Injuries to the reticular activating system within the brainstem could play a role in agitation by impairing arousal and alertness.

Focal brain injury commonly involves contusions to the frontal and temporal lobes based upon how they rest upon the inner table of the intracranial fossae, sphenoid wings, and petrous ridges of the skull. The frontal lobe contains regions of the brain that are responsible for numerous functions, including executive function, attention, emotional processing,

and regulation of impulses and compulsions. Damage and dysfunction in the prefrontal cortex likely play a role in the complex pathophysiology of posttraumatic agitation. For example, veterans with frontal ventromedial lesions have been shown to have significantly higher Aggression/Violence Scale scores when compared to controls and patients with lesions in other brain regions.[16] The temporal lobes contain the amygdala and hippocampus, which impact limbic system functions such as emotion, behavior, and long-term memory. Dysfunction in regulation of the limbic system can potentially result in disinhibited anger and aggression.[17]

The main neurotransmitter involved in the secondary injury cascade is glutamate, released from damaged cells and presynaptic vesicles (Figure 2). Elevated levels of glutamate subsequently lead to changes in cellular calcium and sodium homeostasis. As a consequence of these changes, there is production of oxygen free radicals, mitochondrial damage, and activation of cellular necrosis and apoptosis cascades that can lead to further neuronal damage.[15] Due to the complex and heterogenous process of TBI, localizing cognitive behaviors and agitation to specific areas of injury remains elusive. Posttraumatic agitation may be multifaceted, and likely is the consequence of a combination of different lesions and dysfunction in neurotransmitter systems.

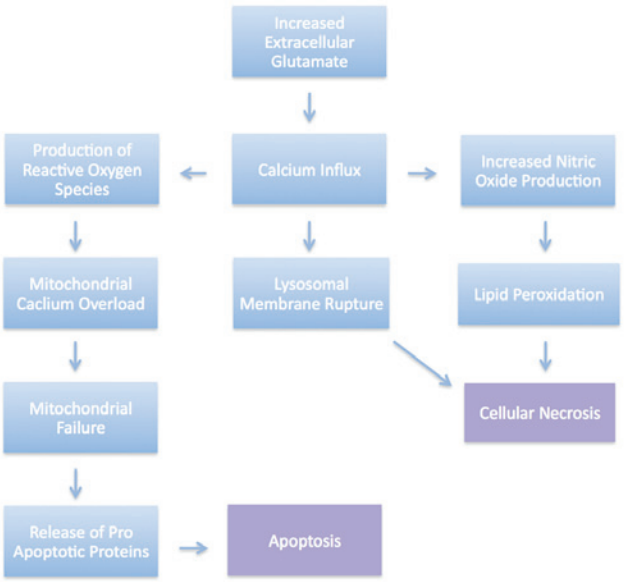


FIGURE 2: **Secondary Injury Cascade in TBI**

Neuronal damage from secondary injury cascades may lead to disruption of intricate neurotransmitter systems that could be the physiologic source for posttraumatic agitation (Figure 2). Much attention has been given to the role of serotonin and dopamine as neurotransmitters involved in such behaviors. Serotonin facilitates prefrontal cortical regions and regulates the emergence of aggressive behaviors by acting on serotonin 5-HT2 receptors in these areas. Loss of serotonergic inhibition in these regions could result in disinhibited aggression and agitation. In a double-blind, randomized, placebo-controlled study of intermittent explosive disorder, treatment with an SSRI resulted in a reduction of aggression and irritability scores, as well as remission of aggressive behaviors in 46% of the 100 patients studied.[18]

Dopamine is an important catecholamine involved in the nigrostriatal, mesocortical, and mesolimbic pathways of the brain. Dopamine receptor antagonists, such as haloperidol, have been used for many years in the management of aggression. Conversely, administration of dopamine agonists, such as amphetamine or apomorphine, results in an increase in aggression in animal models.[19] While the behavioral consequences of neurotransmitter dysfunction following TBI are still not well understood, it is likely that the combination of these disruptions lead to the behaviors characteristic of posttraumatic agitation.

## Treatment Approach

### *Identifying and Measuring Behaviors*

The Agitated Behavioral Scale (ABS) is an assessment tool consisting of 14 behaviors, ranging from emotional lability and impulsiveness to explosive anger and violence, that can be utilized serially to monitor agitation.[20] Using this scale, clinicians can identify patterns of behavior and track outcomes following intervention. The ABS has been demonstrated to have high inter-rater reliability in monitoring agitation in patients with TBI.[21]

### *Physiologic Causes of Agitation*

Acute changes in mental status, including aggressive behaviors and agitation, can be due to a wide range of etiologies following TBI (Table 2); therefore, thorough assessment is required to rule out more serious and potentially life-threatening causes. Hyperadrenergic states are common after TBI, and are marked by tachycardia, hypertension, and agitation. This is largely a diagnosis of exclusion, because such changes in vital signs may be associated with more threatening medical emergencies. For posttraumatic hyperadrenergia, lipophilic beta-blockers such as propranolol are useful.

Agitation also can commonly result from pain. Due to the nature of TBI and associated cognitive deficits, patients may not readily be able to describe pain or its location as the source of their discomfort. It is incumbent on the treatment team to identify and manage potential pain generators such as surgical sites or fractures, tracheostomies, gastrostomy sites, and intravenous lines. Constipation or the need to void also may cause discomfort, and should be considered in patients who are restless or agitated. Imaging should be considered if occult fractures or heterotopic ossification is suspected. Acetaminophen or opioids prescribed on a scheduled or as-needed basis to control pain must be used judiciously to avoid sedating side effects of these medications.

"Sundowning," described as increasing confusion in the evening, should be considered, especially in elderly patients.[22] If needed, a low dose of atypical antipsychotics may be useful for managing behavior. Drug and alcohol withdrawal also should be considered, because it has been estimated that at least two-thirds of TBI patients have a history of substance abuse.[23] If signs of withdrawal are present, institution of a protocol, such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar), for guidance of benzodiazepine administration should be started.

### *Environmental Contributors to Agitation*

Decreasing the level of sensory stimulation from the environment will reduce agitation. Common offending stimuli include ambient noise from medical equipment, television, and background activity, such as nearby staff or visitors. Lowering the lights in the patient's room or in therapy areas can be of benefit. The number of visitors in the patient's room should be limited in order to avoid overstimulating the patient. Conversation in the room should be conducted directly with the patient rather than "around" him. Therapy sessions should be performed in isolation rooms as needed.

Physical restraints must be considered thoughtfully. Although it is important to maintain the safety of all patients, restraints can increase agitation due to their restrictive design. Efforts should be made to limit restraint use; however, there may be occasions when restraints are necessary to maintain patient safety. For example, low beds or enclosure beds can be used if there is a concern for patients rolling or exiting from bed. One-to-one sitters or coaches may be employed in situations where physical restraints are inappropriate or when redirection is necessary.

TABLE 2:

**Differential Diagnoses of Altered Mental Status That May Contribute to Agitation After TBI**

- Noxious stimuli (e.g., lines, constipation, occult fractures, heterotopic ossification, spasticity)
- Posttraumatic hyperadrenergic state
- Infection
- Pulmonary embolus
- Myocardial infarction
- Electrolyte abnormalities
- Hyper- or hypoglycemia
- Sundowning
- Drug withdrawal
- Nonconvulsive seizure
- Endocrinopathy (e.g., SIADH, CSW, DI)
- Medication side effects
- Psychosis or mood disorder

Sleep patterns should be regularly monitored by the use of a daily sleep log tracking the number of hours slept and the pattern of sleep, whether continuous or fragmented. Though disrupted sleep can be due to the brain injury itself, environmental stimuli also can disrupt sleep. If these causes have been addressed and environmental modifications fail to achieve sleep regulation, initiating a sleep aid should be considered. Medications including trazodone, melatonin agonists, and potentially nonbenzodiazepine hypnotics, can be used. The amnestic potential of hypnotic medications, however, can potentially have negative consequences in some patients and should be considered judiciously.

### *Behavioral Plans*

Behavioral plans should be a rehabilitation team effort with input from rehabilitation nursing, therapists, physicians, neuropsychologists, and family. The goals of the behavioral plan include identifying and targeting unsafe or disruptive behaviors, increasing staff identification of antecedent behaviors to anticipate and decrease the rate of targeted behaviors, keeping staff responses to such behaviors consistent, and decreasing the overall frequency of the unsafe or disruptive behaviors. For instance, if the targeted behaviors are hitting and biting, which were preceded by increasing motor restlessness and increased vocal volume, then staff should be made aware of the antecedent behaviors and employ consistent responses to reduce the frequency of hitting and biting.

### *Pharmacologic Intervention*

If agitation continues despite environmental and behavioral modifications, pharmacologic intervention may be considered. A thorough review of the patient's current medications should be performed, and it may be necessary to discontinue drugs that may potentiate agitation, such as narcotics, benzodiazepines, dopamine antagonists such as metoclopramide and prochlorperazine, H2-receptor antagonists such as omeprazole, and anticholinergic agents such as oxybutynin.

Medication interventions to reduce agitation should be used in a goal-directed manner targeting specific aberrant behaviors.[24-26] Mood stabilizers, such as valproic acid or carbamazepine, can be considered as a daily intervention to control behaviors. Interestingly, because agitation may result from an inability to appropriately process sensory information due to impaired neurotransmitter systems, neurostimulants, including amantadine or methylphenidate, can be useful in reducing agitation.[8] Research suggests that typical antipsychotics and benzodiazepines should be avoided due to their negative effects on neurorecovery;[27-28] however, rare, "as-needed" use of atypical antipsychotics (e.g., ziprasidone) or benzodiazepines (e.g., lorazepam) may be necessary in acute situations when a patient is in immediate danger to himself or staff.

## Clinical Vignette Outcome

With proper cognitive and behavioral management, JD was able to complete a comprehensive inpatient rehabilitation program. Propranolol 10 mg tid was used during a portion of her stay for treatment of hyperadrenergia. Her impulsivity was initially managed with an enclosure bed for safety at night, and she was treated with trazodone 50 mg qhs to regulate her sleep/wake cycle. With improved sleep, she was less fatigued and more cooperative during the day. A behavioral plan was created for episodes of physical aggression. During those situations, she was removed from the therapy gym and calmed with redirection and placement in a low-stimulation environment. She did not require any "as-needed" medications for agitation. Her family was educated to avoid overstimulation with visitors. JD was started on amantadine for stimulation, and her participation and attention in therapies slowly improved. She emerged from posttraumatic amnesia and demonstrated good functional recovery. JD progressed from a Rancho Los Amigos level 4 on admission to a level 7 by the time she was discharged to home with her family. She completed her rehabilitative program as an outpatient and has successfully returned to work as a dental hygienist.

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