Agitation After Traumatic Brain Injury

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Outline

- Definitions of post-traumatic agitation
- Pathophysiology
- Differential diagnosis/confounding factors
- Monitoring
- Treatment
  - Environmental
  - Pharmacologic

Rancho Los Amigos
Levels of Cognitive Function

- I – No response
- II – Generalized response to stimulation
- III – Localized response to stimuli
- IV – Confused and agitated
- V – Confused and inappropriate (not agitated)
- VI – Confused and appropriate
- VII – Autonomic and appropriate
- VIII – Purposeful and appropriate
Incidence During Rehab

- Prospective study of 100 consecutive severe TBI admissions to rehabilitation
  - 11% demonstrated agitation by their strict definition
  - Most agitated patients’ behavior resolved in a week
  - 35% were found to be restless

Brooke et al. 1992

Incidence During Rehab

- 158 persons with TBI in an inpatient rehab setting
  - 50% experienced agitation
  - Typically lasted <10 days
  - No significant gender differences in the frequency, duration, presentation, or extent of posttraumatic agitation

Kadyan 2004

Incidence During Rehab

- 28 persons admitted to a brain injury unit with a primary diagnosis of stroke, trauma or anoxia
  - 39% demonstrated aggressive behaviors in the first week of admission
  - Correlation between aggression, disorientation and severity of injury

Galeski et al. 1994
Impact on Rehab

A study of 69 patients with TBI showed that agitated behavior was inversely associated with engagement in rehabilitation therapy
• controlled for injury severity

Lequerica et al 2007

Impact on Rehab

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
• decreased rate of discharge to community
• decreased cognitive FIM scores at discharge

Bogner et al 2001

What is it?

• Hard to define but:
  "I know it when I see it"
  » Justice Potter Stewart, 1964
Survey of AAPM&R
Brain Injury Special Interest Group

- Physical aggression
- Explosive anger
- Increased psychomotor activity
- Impulsivity
- Verbal aggression
- Disorganized thinking
- Perceptual disturbances
- Reduced ability to maintain or shift attention

Fugate et al. 1997

Akathisia

- Constant sense of inner restlessness
  - pacing
  - rocking to and fro
  - fidgeting
  - repetitive actions
  - inability to sit or stay still
- Does not require aggression

Akathisia

- Excessive type 2 dopamine receptor antagonism
  - histaminergic, cholinergic, and adrenergic may also be involved
- Often a side effect of medications
  - antipsychotics
  - antiemetics with antidopaminergic properties
  - selective serotonin reuptake inhibitors
  - tricyclic antidepressants
  - lithium
  - buspirone
  - calcium channel blockers
A Definition

“We suggest that post traumatic agitation be defined as a state of aggression during post-traumatic amnesia. This state occurs in the absence of other physical, medical or psychiatric causes. It can be manifested by intermittent or continuous verbal or physical behaviors.”

-Lombard and Zafonte (2005)

Measuring Agitation

- Scales can be used:
  - objectify agitation
  - monitor success [or failure] of interventions
  - monitor patterns of agitation

Measuring agitation

- Less than half of brain injury specialists use objective measurements of agitation (Fugate 1997)
- Angelino et al (2002) followed Agitated Behavior Scores (ABS) of a 16 yo from coma to wakefulness
  - ABS correlated appropriately both with behavior and with cognitive recovery
Agitated Behavior Scale

- Components each scored from 1 (behavior is absent) to 4 (present to an extreme degree)
- Score ranges from 14-56
- Score ≥ 21 defined to be agitated
- Has been shown to have good inter- and intra-rater reliability

1. Short attention span, easy distractibility and inability to concentrate
2. Impulsive, impatient, low tolerance for pain or frustration
3. Uncooperative, resistant to care, demanding
4. Violent and/or threatening violence toward people or property
5. Explosive and/or unpredictable anger
6. Rocking, rubbing, moaning or other self-stimulating behavior
7. Pulling at tubes, restraints
8. Wandering from treatment areas
9. Restlessness, pacing, excessive movement
10. Repetitive behaviors, motor and/or verbal
11. Rapid, loud or excessive talking
12. Sudden changes in mood
13. Easily initiated or excessive crying or laughter
14. Self-abusiveness, physical and/or verbal
Overt Aggression Scale

- Initially designed for psychiatric patients
- Four domains of aggression
  - Verbal aggression
  - Aggression against self
  - Aggression against people
  - Aggression against objects
- OAS-MNR (Modified for Neurorehabilitation) adds three intervention categories and selecting events that preceded the behavior
The Anatomy of Agitation

• Due to the complex and heterogeneous process of TBI, localizing cognitive behaviors and agitation to specific areas of injury remains elusive

• Posttraumatic agitation may be multi-faceted and likely the consequence of a combination of different lesions and dysfunction in neurotransmitter systems
The Anatomy of Aggression

- Defensive aggression: response to perceived threat
- In cats associated anatomically with hypothalamus, periaquaductal gray, limbic structures

Anatomy of Agitation: Frontal Lobe

- Responsible for:
  - executive function
  - attention
  - emotional processing
  - regulation of impulses and compulsions.

- Veterans with frontal ventromedial lesions have been shown to have significantly higher Aggression/Violence Scale scores when compared to controls

Anatomy of Agitation: Temporal Lobes

- Contain the amygdala and hippocampus which impact limbic system
  - emotion
  - behavior
  - long-term memory

- Dysfunction in regulation of the limbic system can potentially result in disinhibited anger and aggression
Anatomy of Agitation: Temporal Lobes

- Case report of a 14 yo boy who had murdered and was found to have a cystic lesion lateral to his right amygdala (Martinius, 1983)
- Interictal aggression seen in temporal lobe epilepsy

Pathophysiology of Agitation: Serotonin

- Activity in prefrontal cortical regions regulates the emergence of aggressive behaviors
- Loss of serotonergic inhibition can result in disinhibited aggression and agitation.
  - 5HT-1b knockout mice show increased aggression and disinhibition (Bouwknecht et al, 2001)

Pathophysiology of Agitation: Serotonin

- Double blind, randomized, placebo-controlled study of intermittent explosive disorder
  - treatment with an SSRI resulted in a reduction of aggression and irritability scores
  - remission of aggressive behaviors in 46% of the 100 patients studied
Pathophysiology of Agitation: Dopamine

- Involved in the nigrostriatal, mesocortical and mesolimbic pathways of the brain
- Apomorphine (DA agonist) induces aggression in nonaggressive mice
- D2 inhibitors decreases aggression in high-aggressive mouse strains (Nikulina and Kapralova 1992)

Physiology of Agitation: Summary

- Regulation dependent on balance of serotonin and dopamine

Even in the best environment possible...

...identifying and managing agitation can be a challenge
Differential Diagnosis

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

Differential Diagnosis: Drug Withdrawal

- Drug/alcohol withdrawal
  - Alcohol w/d can occur 72 h after last drink
    - Hypertension, tachycardia, disorientation, tremors, agitation
  - Heroin w/d peaks at 24-48 h
    - Restlessness, abdominal pain, yawning
  - Benzodiazepine w/d in 2-7 d, may last weeks
    - Hypertension, tachycardia, diaphoresis, tremors, hyperthermia, seizures

Differential Diagnosis: Pain

Many different potential pain generators:
- other injuries (occult or otherwise)
- spasticity
- heterotopic bone
- tracheostomies,
- gastrostomy tubes
- etc

If pain is an issue, consider using analgesics (scheduled?) and monitor agitation
Nonpharmacologic Management: Sleep
- In the intensive care setting, constant stimulation may lead to day/night confusion
  - 50% of persons admitted to TBI rehabilitation unit report difficulty sleeping (Clinchot et al 1998)
- Treatment Approach:
  - Close monitoring of sleep cycles
  - Quiet nighttime environment
  - Breaks during the day
  - Sleep medications when necessary

Nonpharmacological Management: Managing Overstimulation
Persons with TBI often become overwhelmed in distracting environments
- Education of staff and families is key!!!!
- Limit television use
- Limiting number of visitors
- Limiting visitors’ cell phone use
- Quiet, isolated treatment areas - “Low-stim gym”

Nonpharmacological Management: Using Restraints
Minimally invasive: avoid direct-contact restraints (i.e. wrist restraints, vest restraints)
Nonpharmacological Management

• Try to cover necessary tubing
  – “Out of sight, out of mind”

Nonpharmacological Management

- 1:1 Coach (not sitter) Criteria
  - Harmful to self: pulling vital tubes, suicidal
  - Disruptive to other patients
  - Does not follow weight bearing, helmet precautions
  - Not manageable with cubicle bed / net bed
  - High elopement risk, unable to care for self

Agitation Management: Behavior Plans

Written behavioral plan: staff/ family agreement
- Identify antecedent behaviors
- Quantify acceptable and problematic behaviors
- Environment: special beds, time out, control stimuli
- Redirect behavior: physical activity with coach
- Minimize sedation
- Observe for complex seizures: stereotypic outbursts, large fluctuations in level of consciousness
- Co-Treat for protection
RLA IV: Summary

- Agitation
- Restlessness
- Posttraumatic Amnesia

RLA IV goals

- Re-orientation
- Basic self-care skills focusing on sequencing and staying on task
- Behavior management
- Strength/balance
- May need to be creative about therapeutic treatments

Agitation: Summary

- Confusion and agitation are considered as part of the recovery process from severe TBI
- Often, agitation stems from disorientation and overstimulation.
- Consider other noxious stimuli (pain, infection, feeding tubes, tracheostomies, etc) as contributing to the agitation
Agitation: Nonpharm Treatment Summary

- Non-pharmacological measures
  - putting patient in quiet, dark environment
  - letting patients walk around to burn off energy
- Re-orientation
- Good sleep hygiene

Brain Injury: Agitation Treatment

- Before medicating an “agitated” TBI patient consider:
  - Are they really agitated or just restless?
  - What is the specific unwanted behavior?
  - Are you just treating the staff instead?

Agitation Management: Pharmacology

- Anticonvulsants
- Antidepressants
- Antipsychotics
- Benzodiazepines
- Beta-Blockers
- Lithium
- Neurostimulants
- Others
Anticonvulsants

Valproic Acid (Depakote)
- Used for mania in bipolar disorder
- Dementia related agitation
  - Limited by side effect profile in Cochrane database review

Anticonvulsants: Valproic acid
- Significantly reduced negative behaviors in 1-2 days in 5 persons with TBI related agitation that had not been controlled with other measures
  - Wroblewski et al 1997
- 29 persons with TBI related agitation, 90% responded with decreased agitation after valproic acid within 7 days of treatment
  - Chatham-Showalter et al, 2000

Anticonvulsants: Valproic acid
- The good:
  - Rapid load of 10-20 mg/kg/day
  - Fast onset
- The bad:
  - Hepatotoxicity, thrombocytopenia, elevated ammonia levels, neurocognitive slowing
  - TBI patients metabolize faster, may need larger doses (Anderson et al, 1998)
Anticonvulsants
Carbamazepine (Tegretol)
- Successful use in a case series of 7 TBI rehabilitation inpatients with combativeness
  - Chatham-Showalter et al 1996
- Open label study in 10 TBI patients with agitation
  - Azouvi et al 1999
  - Measured ABS scores and MMSE
  - Good improvement in 5, modest in 3, none in 2
  - No decrease in mental status
  - Improved irritability and disinhibition

Anticonvulsants: Carbamazepine
- The bad:
  - Hyponatremia, renal failure, aplastic anemia
  - Slower titration than valproic acid

Anticonvulsants
- Gabapentin reported to be helpful for dementia-related agitation
  - Case series reported paradoxical effects in 2 patients with TBI
- Lamotrigine and levetiracetam have been suggested
  - No studies at present
  - No blood levels to check
Antidepressants: Tricyclics

- Two groups:
  - More noradrenergic – used for hypoarousal
    - protriptyline (Vivactil)
    - Desipramine (Norpramin)
  - More serotonergic – more sedative
    - amitriptyline (Elavil)
    - imipramine (Tofranil)
- Significant side effect profile:
  - Cardiac, lowered seizure threshold, significant sedation

Success with amitriptyline in a patient with significant frontal lobe damage and aggression
- Jackson et al 1985
- 12 out of 17 TBI patients responded well to amitriptyline
  - Worked best with those still in PTA
  - Mysiw et al 1988

Antidepressants: SSRIs

- SSRI used for several other symptoms in TBI patients:
  - Depression
  - Emotional lability
  - Hypoarousal (questionable results)
- Less seizure and cardiac risk than tricyclics
Antidepressants: Sertraline

- Open-label trial in 13 persons with TBI for 8 weeks
  - resulted in reduced irritability and aggression
  - no reduction in depression
  - Kant et al 1998
- Sertraline treated 15 outpatients with severe depression after mTBI
  - statistically significant improvement in psychological distress, anger and aggression, functioning, and postconcussive symptoms
  - Fann et al 2000

Antidepressants: SSRI

- Timing to efficacy?
  - In depression, takes as long as 2 weeks for effect
  - Unclear timing for agitation treatment

Typical Antipsychotics

- Predominant D2 receptor activity
- Longstanding use for immediate control of agitation due to psychiatric disturbance, sundowning, delirium, and brain injury related aggression
- Haloperidol has been commonly used
  - Rapid onset
  - IM, IV, PO administration
Typical Antipsychotics

Retrospective chart review of 120 persons with TBI in an inpatient rehabilitation unit
- 48% were treated with methotrimeprazine
  - Longer lengths of stay
  - Longer time in PTA
  - Sampling issue?
- 2 had developed extrapyramidal symptoms

Maryniak et al 2001

Antipsychotic Concerns

- Feeney 1982
  - Animal study found slowed motor recovery in an animal model of TBI
- Stanislav 1997
  - Neuropsychological testing improved significantly 1 and 3 weeks after discontinuation of antipsychotics in subjects with TBI
  - Effect was greatest in those taking thioridazine
Atypical antipsychotics

- Treatment of 7 subjects with aggression after sustaining a TBI with quetiapine (Seroquel)
  - Dosages from 25 mg to 300 mg daily
  - Overt Aggression Scale scores significantly decreased
  - Noted improvement in cognitive functioning

Kim and Bijlani 2006

Atypical Antipsychotics

- Ziprasidone (Geodon) used in 5 persons with severe TBI and agitation
  - Within 2 weeks ABS decreased from 27.2 to 18
  - Treatment range of 35-68 days
  - No side effects noted

Noe et al. 2007
Antipsychotic concerns

- Reports of neuroleptic malignant syndrome in persons with TBI:
  - Kadyan et al. 2003
  - Wilkinson et al. 1999
  - Vincent et al. 1986

Typical versus Atypical

- Kline et al 2007
- Induced TBI in rats, who were then treated with either single doses or chronic treatment with haloperidol, risperidone or vehicle
  - Single doses of either agent did not depress performance in beam walking or Morris water maze
  - Daily doses of either risperidone or haloperidol did significantly reduce performance
  - Deficits still present after a 3 day washout period

Typical versus Atypical

- Wilson et al 2003
- Studied Morris water maze performance in rats after induced TBI
  - Groups were given daily injections of haloperidol, olanzapine, or vehicle and tested 11-15 days after injury
  - Group treated with haloperidol performed significantly worse than vehicle-treated rats
  - Olanzapine group did not show the decrement in performance seen in haloperidol group
Benzodiazepines

- General indications
  - Sedation in intensive care unit
  - Sedation for surgical procedures (amnestic effect)
  - Alcohol or drug withdrawal
  - Acute mania
  - Treatment of neuroleptic-induced akathisia
  - Spasticity management

- Paradoxical agitation can be seen with administration
- Naturally cause an amnestic effect

- Early and daily administration of diazepam impaired motor recovery in rats with cortical lesions
  - Schallert et al 1986
- Case series of 8 persons with a distant history of stroke given light sedation with midazolam had transient reappearance of neurologic symptoms
  - Lazar et al 2002
Benzodiazepines

- Potential utility in TBI population
  - Alcohol withdrawal
  - Sedation for procedures
  - Emergency/rescue medication

Beta blockers

- Other indications:
  - Alcohol withdrawal
  - Hyperadrenergic state
  - Neuroleptic induced akathisia
  - Lipophilic agents (propranolol) might be more centrally acting
  - Cochrane database review cited beta blockers as having the best evidence for treatment of TBI related agitation
    - Fleminger et al 2003

- Low dose propranolol decreased agitation, aggression and wandering in dementia patients
  - Shankle et al 1995
  - Pindolol reduced violent behaviors in 8 out of 13 TBI patients in a placebo controlled trial
    - Reduced care needs in some due to improved behavior
    - Greendyke et al 1989
Lithium
- One of the oldest treatments for bipolar disorder
- Method of action is unclear
  - Alters sodium transport
  - Increases intracellular metabolism of catecholamines
  - Questionable DA blocking effects

Side effects include:
- Movement disorders, seizures, hypothyroidism, bradycardia, vomiting
- Toxicity level (>1.4 mEq/L) is very close to therapeutic range (0.6-1.2 mEq/L)
- Patients need close monitoring by practitioners experienced in titrating this medication

Lithium
- 10 inpatient TBI rehabilitation patients were given lithium for severe aggression
  - 5 experienced a significant improvement with increased participation in rehabilitation
  - 3 had such significant side effects that they needed to discontinue it
  - Glenn et al 1989
Neurostimulants

- Agents for enhancing awareness and cognition
- Can improving focus and decreasing confusion lead to less agitation?
  - Potential for overstimulation
  - Caution for sleep dysregulation with more activating agents

Neurostimulants: Amantadine

- Reduced agitation in 7 of 19 persons with dementia
  - Significant side effects including overactivity, anxiety and visual hallucinations were seen in 8 of the subjects
  - Muller et al 1979
- Several small case series in persons with TBI showed amantadine reduced agitation
  - Rosati 2002; Chandler et al 1988; Nickels et al 1994

Neurostimulants: Amantadine

- Survey of TBI specialists in the AAPM&R
  - Amantadine was found to be the preferred agent for agitation in patients with TBI
  - Fugate et al 1997
Neuro stimulants: Methylphenidate

- TBI related anger of 38 persons was significantly reduced with 30 mg methylphenidate daily
  - Mooney and Haas, 1993

Step 1: Identify unwanted behaviors and measurables
Step 2: Consider differential diagnosis
  - Drug withdrawal
  - Infection
  - Pain
  - Hypoxia
  - Seizure disorder
Step 3: Assure adequate sleep regulation
Step 4: Consider environmental issues
  - Low-stimulation environment
  - Reduction of physical discomfort/lines/restraints
  - Reorientation/1:1 Coach
  - Behavior Plan
Step 5: Medication Management (scheduled and/or prn)

Questions?