Agitation after TBI: Current Concepts of Pathophysiology, Assessment and Treatment

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GOALS OF PRESENTATION

- Review “Levels” of Neurocognitive Function
- Discuss Rancho Los Amigos Stages of Cognitive Recovery
- Demonstrate how the Rancho Los Amigos Stages correspond with Neuroanatomical Functioning
- Discuss how Agitation relates to functional neuroanatomy in the brain injured patient
- Define Agitation
- Differentiate Agitation from other behavior
- Define other behavioral states confused with agitation
- Differential Diagnosis
- Non-pharmacologic management of agitation
- Pharmacologic management of agitation
WHAT IS THE PURPOSE OF THE BRAIN?
HOW ABOUT THESE GUYS?
DIAGRAM OF BASIC BRAIN FUNCTION

COGNITIVE FUNCTION

Sensory Input

Motor Output
PYRAMID OF COGNITIVE FUNCTION

- EXEC FXN
- MEMORY
- ATTENTION
- PROCESSING SPEED
- AROUSAL/ALERTNESS
DIAGRAM OF BASIC BRAIN FUNCTION

- Sensory Input
- Arousal/Alertness
- Processing Speed
- Attention
- Memory
- Executive Function
- Mood
- Motor Output
RANCHO LOS AMIGOS STAGES OF COGNITIVE RECOVERY (ORIGINAL)

LEVEL 1 – NO RESPONSE
LEVEL 2 – GENERALIZED RESPONSE
LEVEL 3 – LOCALIZED RESPONSE
LEVEL 4 – CONFUSED/AGITATED
LEVEL 5 – CONFUSED, INAPPROPRIATE
LEVEL 6 – CONFUSED, APPROPRIATE
LEVEL 7 – AUTOMATIC, APPROPRIATE
LEVEL 8 – PURPOSEFUL, APPROPRIATE
CORRELATION BETWEEN RLAS AND LEVELS OF COGITIVE FUNCTION

LEVEL 8 – PURPOSEFUL, APPROPRIATE
LEVEL 7 – AUTOMATIC, APPROPRIATE
LEVEL 6 – CONFUSED, APPROPRIATE
LEVEL 5 – CONFUSED, INAPPROPRIATE
LEVEL 4 – CONFUSED/AGITATED
LEVEL 3 – LOCALIZED RESPONSE
LEVEL 2 – GENERALIZED RESPONSE
LEVEL 1 – NO RESPONSE
THE RETICULAR FORMATION

- Radiations to cerebral cortex
- Visual impulses
- Reticular formation
- Auditory impulses
- Ascending general sensory tracts (touch, pain, temperature)
- Descending motor projections to spinal cord
CORRELATION BETWEEN RLAS AND LEVELS OF COGNITIVE FUNCTION

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THE LIMBIC SYSTEM

COMPONENTS IN THE DIENCEPHALON
- Corpus callosum
- Fornix
- Pineal gland
- Cingulate gyrus
- Parahippocampal gyrus
- Hippocampus
- Anterior group of thalamic nuclei
- Hypothalamus
- Mamillary body
- Amygdaloid body
CORRELATION BETWEEN RLAS AND LEVELS OF COGNITIVE FUNCTION

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MEMORY FUNCTION
CORRELATION BETWEEN RLAS AND LEVELS OF COGNITIVE FUNCTION

LEVEL 8 – PURPOSEFUL, APPROPRIATE
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EXECUTIVE FUNCTION
WHAT DOES THIS ALL HAVE TO DO WITH AGITATION?
AGITATION - DEFINITION

ag·i·ta·tion [ˌajəˈtāSH(ə)n]  
NOUN  
ORIGIN
mid 16th cent. (in the sense ‘action, being active’): from Latin agitatio(n-), from the verb agitare (see agitate).

1. a state of anxiety or nervous excitement:
   "she was wringing her hands in agitation"
2. the action of arousing public concern about an issue and pressing for action on it:
   "widespread agitation for social reform"
3. the action of briskly stirring or disturbing something, especially a liquid.
AGITATION – MEDICAL DEFINITION

A state of excessive psychomotor activity accompanied by increased tension and irritability

- Merriam Webster

A state of restless anxiety. Clinically increased nonpurposeful motor activity, usually associated with internal tension

CHARACTERISTICS OF CLASSIC AGITATION

- Psychomotor restlessness
- Non-purposeful activity
- Associated with anxiety, tension, fear, irritability
- These are related to INTERNAL state of mood, etc.
- NOT related to external events, necessarily
CHARACTERISTICS OF THE CLASSICALLY AGITATED PATIENT

- Still exhibiting a degree of impaired arousal
- Basis of agitation is slowed cognitive processing speed, resulting in SENSORY OVERLOAD
- Underlying emotional state is ANXIETY or FEAR
- Exhibiting motor restlessness that is usually independent of specific environmental stimuli
AGITATION IS NOT NECESSARILY:

- Anger
- Aggression
- Irritability
- Refusing to cooperate
- Purposeful
DEFINITIONS
POSTTRAUMATIC AGITATION-

Related to the posttraumatic amnesia period. Decreases as cognitive functions improve.

Combination of aggression, akathisia, disinhibition, emotional lability, motor restlessness, impulsivity, disorganized thinking, perceptual disturbances, impaired attention.
AGGRESSION-

- verbal aggression
- physical aggression against objects
- physical aggression against self, other persons
- severe irritability, violent, hostile, or assaultive behavior and “episodic dyscontrol”
- i.e. cursing at others, screaming/yelling, breaking/throwing things, being arrested, hitting/pushing others, threatening to hurt others
AGGRESSION

Characteristic features after TBI:

• Reactive- Triggered by modest of trivial stimuli
• Nonreflective- Usually does not involve premeditation
• Nonpurposeful- Aggression serves no obvious long-term aims or goals
• Explosive- Buildup is NOT gradual
• Periodic- Brief outbursts of rage and aggression punctuated by long periods of relative calm
• Ego- dystonic- After outbursts, patients are upset, concerned, and/or embarrassed, as opposed to blaming others or justifying behavior
IRRITABILITY -

• excessive reaction with unjustified fits
• i.e. having and increased number of arguments/ fights, making quick impulsive decisions, complaining, cursing at self, feeling impatient, or threatening to hurt self
BEHAVIOR AND COGNITION

- Damage to dorsolateral prefrontal subcortical circuits
  - Many challenging behaviors flow from impaired cognition
    - Poor judgement
    - Impaired problem solving
    - Set shifting
    - Complex attention
    - Impulsivity
    - Impaired Awareness
DIFFERENTIAL DIAGNOSIS OF AGITATION AND AGGRESSION

- Brain Injury: But what else?
- Medications, alcohol, and other abused substances, and over-the-counter drugs
- Delirium (hypoxia, electrolyte imbalance, anesthesia and surgery uremia, etc.)
- Infectious diseases (encephalitis, meningitis, pneumonia, UTI)
- Sleep/wake cycle inversion
- Epilepsy (ictal, postictal, interictal)
- Pain (trach, PEG, sores, constipation, musculoskeletal, etc.)
- Metabolic disorders (hypothyroidism, or hyperthyroidism, hypoglycemia, vitamin deficiencies)
- Alzheimer’s disease
AGGRESSION ASSOCIATED WITH EPILEPSY

Temporal lobe epilepsy:

- Interictal aggression characterized by behavior justified on moral or ethical grounds
- Ictal or postictal characterized by violent behavior with non-directed quality and presence of altered level of consciousness
- Not associated with specific EEG patterns
MEDICATIONS AND DRUGS

- **Alcohol**: intoxication and withdrawal states
- **Hypnotic and antianxiety agents (barbiturates and benzos)**: intoxication, withdrawal and paradoxical reactions
- **Analgesics (opiates and other narcotics)**: intoxication and withdrawal states
- **Steroids** (prednisone, cortisone and anabolic steroids)
- **Antidepressants**: especially in initial stage of treatment
- **Amphetamines and cocaine**: aggression with manic excitement in early stages of abuse and secondary to paranoid ideation in later stages of use
- **Antipsychotics**: high-potency agents that lead to akathisia
- **Anticholinergic drugs (including over-the-counter sedatives)** associated with delirium and central anticholinergic syndrome
FIGURE 14-4. Neuropsychiatric factors associated with agitation and aggression.

Silver et al. 2013
PREDICTORS OF AGITATION AFTER TBI

- Looking at predictors of agitated behavior during rehabilitation
- Prospective longitudinal study- TBI PBE study
- ABS scores
  - Infection and lower FIM cog scores predicted more severe agitation
  - More severe agitation predicted more severe agitation in the future
  - Lack of a significant relation premorbid psychiatric disorders (e.g., those involving mood regulation).

Bogner J, et al. 2015
PREDICTORS OF AGITATION AFTER TBI

- Medication classes associated with more severe agitation:
  - sodium channel antagonist anticonvulsants:
    - primarily valproic acid, phenytoin, and carbamazepine
  - second-generation antipsychotics
    - primarily quetiapine, risperidone, and ziprasidone
  - gamma-aminobutyric acid-A anxiolytics/hypnotics
    - primarily lorazepam
  - Medications that cause sedation or cognitive impairment worsen agitation?

Bogner J, et al. 2015
PREDICTORS OF AGITATION AFTER TBI

• Medication classes associated with less severe agitation:
  • Antiasthmatics
    • primarily albuterol and to a lesser extent ipratropium bromide
  • Statins
  • Norepinephrine-dopamine-5 hydroxytryptamine (serotonin) agonist stimulants
    • primarily methylphenidate
  • wakefulness-promoting stimulants
    • modafinil, armodafinil

Bogner J, et al. 2015
PREDICTORS OF AGITATION AFTER TBI

• Not significant in model but frequently used ($p < .15$):
  • serotonin antagonist and reuptake inhibitor antidepressants (trazodone)
  • N-methyl-Daspartate antagonists (amantadine)

Bogner J, et al. 2015
MANAGING AGITATION

• History and physical-
  • Premorbid- history- psychiatric, behavior history, substance abuse
  • Differential diagnosis

• Combination behavioral, environmental, psychotherapeutic, psychopharmacologic evaluations and interventions

• Educated and experienced staff

• Tolerating some level of agitation- non-dangerous

• Difficulty filtering and prioritizing stimuli- important of low stimulation environment
MANAGING AGITATION

• Behavioral plan:
  • Multidisciplinary approach to evaluating behaviors- triggers, frequency, intensity
  • Antecedents, Behavior and Consequence
  • Pro-active: Create plan on how staff should act before behaviors start
  • Positive and negative reinforcement
  • Sensitivity to changes in routine
  • Using predictability of response to shape positive behaviors
  • Include family in plan
  • Main variable to manipulate is the behavior of other people
INCOG RECOMMENDATIONS FOR MANAGEMENT OF COGNITION FOLLOWING TRAUMATIC BRAIN INJURY: PATIENTS IN POSTTRAUMATIC AMNESIA/ DELIRIUM

• Consistent environment by people who understand their needs
• Avoid restraint and allow person to move around freely
• Maintain a quiet and consistent environment on ward
• Avoid overstimulation- auditory, visual, environment
• Evaluate the impact of visitors, assessment, and therapy and limit if causing agitation or excessive fatigue

INCOG RECOMMENDATIONS FOR MANAGEMENT OF COGNITION FOLLOWING TRAUMATIC BRAIN INJURY: PATIENTS IN POSTTRAUMATIC AMNESIA/DELIRIUM

• Allow rest as needed
• Have consistent staff dealing with the patient
• Establish most reliable means of communication
• Provide frequent reassurance
• Present familiarizing information as tolerated by the person
• Help family members understand PTA and how to minimize triggering agitation

MEASURING AGITATION AND AGGRESSION

- Agitated Behavior Scale (Corrigan and Bogner 1994)
  - 14 different behaviors
- Overt Agitation Severity Scale (Yudofsky, et al. 1997)
  - Vocalization and Oral/ Facial Movements
  - Upper Torso and Upper Extremity Movements
  - Lower Extremity Movements
- Overt Aggression Scale (Yudofsky, et al. 1986)
  - Help define and document aggression
  - Verbal Aggression
  - Physical against self, objects, other people
  - Intervention
  - Modified Version- Quantitative vs. Qualitative
The premise that a quiet patient is a good patient is an unsound one in rehabilitation, as active participation in treatment is a prerequisite for improving function and promoting recovery.

Flanagan, Elovic 2009
PHARMACOLOGIC INTERVENTIONS

• Second-line of treatment
• Start low and go slow
• Provide adequate therapeutic trial
• Recognize this is a dynamic state- recovery
• Perform continuous reassessment
• Set targets for success
• Monitor drug-drug interactions
PHARMACOLOGIC INTERVENTIONS

• Neurochemical changes in:
  • Catecholaminergic deficit
    • Arousal, attention, memory, motivation, mood regulation
  • Cholinergic deficit
    • Cognition (attention and memory), behavior
  • Serotonergic deficit
    • Modulation of normal mood state and aggression
COCHRANE REVIEW

• To evaluate the effects of drugs for agitation and/or aggression following acquired brain injury
• They independently extracted data and assessed trial quality
• Randomized controlled trials (RCTs) that evaluated the efficacy of drugs acting on the central nervous system for agitation and/or aggression, secondary to ABI, in participants over 10 years of age
• Studies of patients within six months after brain injury and/or in a confusional state, were distinguished from those of patients more than six months post-injury, or who were not confused

Fleminger S, 2008
COCHRANE REVIEW

- This review found no firm evidence that drug management of agitation and aggression in adults with acquired brain injury is effective.
- There was weak evidence, based on a few small randomized controlled trials, that beta-blockers can improve aggression after acquired brain injury.
- Firm evidence that carbamazepine, valproate or amantadine were effective in the management of agitation and/or aggression following ABI was lacking.
- Numerous drugs have been tried in the management of agitation in ABI but without firm evidence of their efficacy.
- It is therefore important to choose drugs with few side effects and to monitor their effect.

Fleminger S, 2008
BETA- BLOCKERS

• Mechanism:
  • Lipophilic agents like propranolol reduce hyperadrenergic activity
• Rationale for using beta-blockers is the reduced adrenergic activity at central or peripheral level.
• Efficacy four controlled studies vs. placebo that used either propranolol or pindolol
• Except for one study (Brooks, et al 1992) population is ABI
• Brooks 1992 study: 21 patients subacute phase post TBI
  • Propanolol versus placebo
  • Propranolol starting at 60 mg to max of 420 mg
  • Significant reduction in aggression with max effect at 5 weeks
BETA- BLOCKERS

- TBI patient with hypertension
- Propranolol start at 20 mg per day
- Titrate dose to 40-80 mg per day
- Has been used as high as 540 mg per day
- Needs to be weaned
- Consider baseline ECG
- Limited by bradycardia and hypotension
- Stop treatment at 8 weeks if no effect

MOOD REGULATING ANTIEPILEPTICS

- valproic acid, carbamazepine, oxcarbazepine, lamotrigine
  - Among potential mechanisms, they are thought to act by inhibiting GABA
  - Level of evidence is quite modest
  - Heterogenous populations
  - Consider for associated epilepsy or bipolar disorder
  - Noted risk of cognitive effects from carbamazepine
MOOD REGULATING ANTIEPILEPTICS

• Valproic Acid:
  • Starting dose: 250 mg bid (dosing range 1500-4500mg per day)
  • Side effects: nausea, sedation, weight gain, rash, hepatic impairment, hair loss, thrombocytopenia

• Carbamazepine:
  • Starting dose: 100 mg (dosing range 200-1,600mg daily)
  • Side effects: blood dyscrasias, SIADH, hepatic impairment, rash
PSYCHOTROPIC MEDICATIONS

• 1st generation antipsychotics (Haldol): strong D2 antagonist- blockage in the striatal D2 receptors- antipsychotic effect
  • Prolonging PTA in humans
  • Worse motor and cognitive outcomes in animal models
  • D2 receptor blockade in the mesocortical and nigrostriatal pathways
  • Sedative properties are sometimes employed to control problematic behavior
PSYCHOTROPIC MEDICATIONS

• Atypical antipsychotic (risperidone, olanzapine, quetiapine, ziprasidone):
  • also inhibit the D2 receptor but also serotonergic 5HT2A, 5HT2C, dopaminergic D1, D4, histamine, alpha-1 adrenergic, and muscarinic receptors
  • Improved safety profile
  • Reduced incidence of extrapyramidal side effects
  • Animal models showing that atypicals do not disrupt cognitive recovery after TBI
  • Limited human data
  • Use with caution
PSYCHOTROPIC MEDICATIONS

• Risperidone:
  • Starting dose 0.5mg PRN
  • Side effects: sedation, akathisia, metabolic impairment

• Quetiapine:
  • Starting dose: 25mg (dose range 300-800 mg per day)
  • Side effects: sedation, anticholinergic

• Olanzapine:
  • Starting dose: 2.5 mg PRN
  • Side effects: sedation, rash, metabolic impairment, weight gain, hypotension, dizziness, paradoxical arousal at low doses

• Ziprasidone:
  • Starting dose: Oral- 20 mg, IM- 10mg PRN
  • Side effects: Q-T prolong, hypotension, dizziness, electrolyte disturbance, metabolic changes, akathisia
AMANTADINE

- Mechanisms of action:
  - Increases dopamine both presynaptic postsynaptic
  - Inhibits the NMDA receptor
  - Serotonergic action on mood regulation
  - Stimulate neurotrophic factors in animal model
- Justification for agitation primarily cognitive
- Recent study by Hammond, et al 2017 looking at aggression and anger
  - Follow up of previous study showing effect on irritability in post acute sample
  - Decreased aggression from prospective of TBI survivor
  - No effect on anger
- Starting dose 100 mg daily (dose range 50-200 mg daily)
- Side effects: Psychosis in particular elderly, dizziness, insomnia, nausea
ANTIDEPRESSANTS

• SSRI’s, SSNRI’s, non-tricyclic, non-MAOI
• Why?
  • Modulation of serotonin, dopamine and noradrenaline
  • Animal studies showing inverse relationship of serotonin and aggression
  • Depression and anxiety are part of and can worsen agitation
• Delayed effect onset of action
• Most literature on sertraline
  • Starting dose: 25 mg (dose range 25-200mg)
  • Side effects: nausea, diarrhea, SIADH, agitation, insomnia
• Commonly used sleep agent after TBI
  • Starting dose: 25 mg PRN
  • Side effects: sedation, priapism, hypotension
  • Dose range 25 -150 mg
METHYLPHENIDATE
• Psychostimulant increasing dopamine and norepinephrine
• Acts on agitation and aggression through pro cognitive effect
• Positive effect on impaired or fluctuating arousal
• Quick acting antidepressant effect
• A number of small studies showing effect on aggressiveness
• Risk of agitation and irritability
  • Starting dose: 5mg (dose range 5-60mg per day)
  • Side effects: anorexia, insomnia
BUSPIRONE

• Serotonin 1A receptor agonist
  • Anxiety after TBI- small case studies
  • No known adverse cognitive side effects
  • Not effective acutely
  • Benefits delayed 2-3 weeks
  • Starting dose: 5 mg bid (dose range 20-30/ day bid-tid)
  • Contraindicated with MAOI’s
BENZODIAZEPINES

• Commonly used in acute escalation of violent behavior
• Generally avoided for prolonged use due to cognitive and sedative side effects and paradoxical agitation
NUDEXTA (DEXTROMETHORPHAN/QUINIDINE)

- Primary indication- Pseudobulbar affect
- Off label agitation
- Dextromethorphan (DM) - The exact mechanism of action of the drug is not known completely, but it is believed to work by regulating excitatory neurotransmissions through the sigma-1 receptor agonist activity and NMDA receptor antagonist activity.
- Quinidine- inhibits breakdown of DM by inhibiting CYP2D6

Looking for an organic etiology:
- pain
- infection
Drug withdrawal
Adverse effect of treatment

Adaptation of the environment
- Reducing physical restraints
- Room with personalized objects
- Low stimulation environment

Ensuring good sleep cycle regulation
Medication management

Critical situation
- Neuroleptics
- and/or benzodiazepines
- Limited duration of treatment

First line treatment regimen
- Mood stabilizers anti-Epileptics and beta-blockers (no marketing authorization)

Second line Treatment regimen
- Antidepressants or atypical neuroleptics (no marketing Authorization)

Lombard and Zafonte, 2005
SUMMARY

- Understanding of definition and components of agitation
- Environmental interventions
- Educated staff
- Targeted pharmacologic interventions
- Frequent evaluation for efficacy, side effects and ongoing need for intervention
THANK YOU