Post Traumatic Brain Injury: Factors Involved in the Physical and Emotional Recovery

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TBI Overview
- Three million people suffer TBI each year in the United States.
- Psychosocial deficits can be a major factor in the disability.
- Losses in many areas: functional, educational, family, interpersonal.
- Extreme changes in mood and personality occur which demand treatment.
- Lack of recognition of the psychiatric sequelae may lead to deficient treatment.
- Genetic factors may play a role in brain recovery. These factors may be beyond our control as providers in the healing process.
- Total lifetime comprehensive costs of TBI: 21 Billion dollars!! (2009 estimate)

Genetic Factors Involved in Recovery
- Do you wonder why outcomes are so variable and hard to predict?
- Genetic sciences have greatly changed making it possible to sequence genomes and understand more fully genetic variations.
- Genetic differences in patients may affect response to brain injury in terms of chemical changes that occur in the brain i.e. destructive vs. healing chemicals.
Responses to Neurological Injury: Activation of Genes

- Initially there may be gene activation leading to expression of stress proteins, nerve growth factors such as BDNF, glial cell neurotrophic factor.
- Genetic factors may play a role in the level of injury extent, recovery response, pre-injury traits, behavioral disorders.
- All of these factors occur due to a very complex system of polygenic control.

Injurious Effects: Possible Genetic/Biochemical Causes

- Excitatory Amino Acids. Excessive Glutamine and Aspartate release may be associated with neuronal death. Genetic variability may affect injury response.
- Protease Activation. Calpains and Caspasases are involved in cell death. Calpains breakdown elements of microtubules and filaments in the brain. Caspasases play a role in cell death through alteration in repair of cellular DNA.
- Inflammation. Can effect brain tissues, alter the blood-brain barrier, and the sequences of injury to the brain. Cytokines regulate inflammatory response, both pro and anti. Research data suggests genetic polymorphism in Cytokines may affect TBI outcome. Interleukin 1 and 6 are inflammatory cytokines which might affect hemorhage and reduced hippocampal neurogenesis.

Genetic Effects of Repair and Regeneration

- Neurogenesis can occur!!! Fibroblast growth factor-2, epidermal growth factor, sonic hedgehog gene and serotonergic activity all may affect regeneration.
- BDNF: Brain-Derived Neurotrophic Factor, necessary to the formation and maintenance of memory. Elevated almost immediately after a brain injury. Polymorphism in BDNF gene may impact cognition.
- Apolipoprotein E. Neuronal repair and plasticity after TBI. E4 allele, however, is associated with poor outcomes of memory and may possibly increase the risk of post-TBI development of Alzheimer’s Disease.
- Monoamines, Catechol-O-Methyltransferase
- Very early stage of exploration. Genes may play roles in brain’s response to trauma, repair and recovery/outcome. This could explain the variability in recovery.
Mood Disorders After TBI

- Prevalence rates vary in studies. Hibbard study showed Major Depression in 61% of TBI patients.
- Mania has also been reported but far less studied. Possible link to post-traumatic seizures of partial complex type (temporal lobe epilepsy) Bracken et al.
- Major Depression also highly associated with anxiety (over 70%) and aggression (over 50%) Jorge, Robinson
- Pathological Laughing and Crying may be as high as 10%. Tateno 2004
- Pre-injury substance abuse and mental illness may increase rates of Post TBI mood disorders

Neurotransmitter Chaos

- Choline deficits may affect memory in forebrain and possibly with amnesia, amnestic, agitation and disinhibited behavior
- Aggression, mood and anxiety may be related to Serotonin abnormalities
- Dopamine may also be affected leading to executive dysfunction, memory, apathy
Anatomical Changes of TBI Patients with Mood Disorders

- Major Depression was associated with reduced gray matter volume in the lateral aspects of the left prefrontal cortex (Jorge et al. 2004)
- Animal models suggest cell loss can occur over weeks to months. This may be immediate or delayed
- High levels of amygdala activation may be associated with anxiety and negative affect (Danysz 2002)
- Hippocampal volume loss was seen in patients with mood issues
- Severity of TBI correlated with severity of mood issues
- Depression without TBI may also affect brain loss thus the double hit
- Speculated that early administration of antidepressants might prevent progression of functional and mood issues
Treatment of Mood Disorders

- Lack of controlled studies to prove effect of medications
- TBI patients can be very sensitive to meds thus “start low and go slow”
- Older tricyclic class of antidepressants have been shown to be effective (Desipramine and Nortriptyline) but they do have many side effects. May help with anxiety, anger, aggression
- SSRI Zoloft has been shown to help cognitive functioning (Fann 2001). Celexa also showed good efficacy (Rapoport 2008)
- Be cautious of anticholinergic effects, sedation and potential for seizures
- Mood stabilizers such as Lithium, Depakote, Tegretol not well studied
- Psychotherapy essential part of the treatment
- ECT is not contraindicated. Most likely use very low energy and non dominant side of brain

Psychosis and TBI

- TBI patients have a two to five fold risk of being psychotic and patients with psychotic disorders are more likely to have had a TBI
- Pre morbid psychological issues, left hemispheric and temporal lobe injury and severity of TBI are risk factors for psychosis
- Paranoid delusions and hallucinations are the main symptoms
- Amnesia, severe mood disorders and medication effects might be the cause
- Seizures, substance abuse and Depression MUST be considered
- Medications must be used with caution. Some studies show effecting dopamine can impede recovery (park, arousal, Parkinsonism)
- Tardive dyskinesia may be more of a risk
- Newer atypical antipsychotic meds might be safer to use

Post Traumatic Stress and TBI

- PTSD may manifest with symptoms of high anxiety, reliving a traumatic event, nightmares, flashbacks, avoidance and hyper arousal
- Combat data indicates increased incidence of PTSD in injuries with TBI
- Both TBI and PTSD may result in similar chemical abnormalities
- There may be genetic links to vulnerability of PTSD following trauma
- Prefrontal cortex, ventral frontal lobe and anterior temporal lobe damage may be evident in TBI and PTSD
- Co morbidity may effect outcome
- Treatment includes Cognitive Behavioral Treatment, stress management
- Medications, no FDA approved: SSRI, atypicals, Prazosin, Cyproheptadine (off label)
Personality Changes with TBI

- Loss of sense of self
- Childish behaviors
- Impaired judgement, behavior and social awareness
- Aggression and irritability
- Affective lability
- Attention
- Language Deficits
- Perception
- 70% of TBI patients sustain frontal lobe injury

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<tr>
<th>TABLE 10-1: Brain regions associated with personality traits</th>
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Source: Adapted from Fassier et al.
Aggression after TBI

- Major source of distress to patients and stress to families
- In the acute phase of TBI there may be risk to patients and care providers
- Irritability and temper issues persist after acute phase
- Pre-morbid personality issues, substance abuse, Major Depression and frontal lobe injuries are risk factors
- Damage to the amygdala may result in violent behavior
- Alcohol, benzodiazepines, opiates, steroids, antidepressants in early stage of tx, amphetamines, antipsychotics of high potency, anticholinergics (Benadryl) may all induce aggression

Other causes of Aggression

- Medications (blood pressure, Sinemet, anticonvulsants)
- Delirium: underlying infection, electrolyte issues, hypoxia, anesthensia
- Alzheimer’s Disease
- Infection
- Epilepsy
- Thyroid, calcium, vitamin issues

Alcohol and Drug Disorder Issues

- Greatest risk for TBI: Period!!
- 30 to 50% of TBI patients test positive for alcohol on admit
- Other drug abuse not well studied
- They are also at greater risk for a second alcohol related TBI (Winkel et al. 2008)
- 50% of fatal accidents in USA are MVA and 50% associated with alcohol/drugs
- Drug and alcohol abuse may lead to drug interactions, seizures, psychosis, depression and drug seeking behavior
- Monitor for withdrawal as it may be deadly
- AA/NA and substance abuse tx of vital importance. Discuss high risk of TBI before it even happens
Treatment Options

- Family therapy: Focus on reintegration, placement/redesign home, drastic lifestyle changes, caregiver fatigue, legal issues. Mood disorders may be as high as 66% in family.
- Psychotherapy: Cognitive Behavioral models, supportive, behavioral interventions, dealing with loss, managing catastrophic reactions, try to understand the experience and guide through it.
- Psychopharmacology and complementary therapies.

Psychopharmacology

- Stretching and straining of brain tissue can cause massive release of brain neurotransmitters, Glutamate, L-aspartate, GABA, Dopamine, Serotonin, Norepinephrine thus the "neurotransmitter storm". These levels then reduce.
- Glutamate through effects on receptors may increase calcium, activate enzymes, increase glucose utilization resulting in high lactate.
- Need more studies to evaluate use of Namenda and Amantidine.
- Other neurotransmitter abnormalities may increase psychiatric sequelae.
- Anticonvulsants frequently used in acute phase. May be neuroprotective but can also cause memory issues and aggression. TBI patients may be at risk for seizures for years post injury. Prophylaxis may be stopped after first week but be mindful of reoccurrence of seizures.

Pharmacotherapy Concerns

- Families worry about their loved one having a "mental illness".
- Reduce stigma by emphasizing neurobiological aspect of the illness.
- Meds may interfere with "natural healing".
- Fears of addiction.
- Start low and go slow, good trial of medication, watch for drug interactions, augment strategies, symptom intensification.
- Seizure risk.
Treatment of Syndromes

- **Cognitive Improvement:** Stimulants such as Ritalin or Adderall. Also, Aricept or Exelon may enhance memory.
- **Depression:** Treatment might not only help mood but aggression and irritability too. SSRI such as Cefixa, Zoloft, Lexapro have limited drug interactions and can be effective. SNRI such as Effexor or Cymbalta may help mood and pain issues. Caution with Wellbutrin with possible suicide risk.
- **Mania:** Extremely rare. Depakote, Tegretol, Zyprexa, Seroquel, Lithium. Increased confusion and side effects likely with all.
- **Pathological Laughing and Crying:** Moment to moment variability. SSRI, Nuedexta or Amantadine.

Treatments Continued

- **Anxiety and PTSD:** SSRI, Buspar or possibly Benzodiazepines (watch for disinhibition or memory loss)
- **Psychosis:** Mood may help but could slow recovery. Haldol can be used but older meds may increase falls, tardive dyskinesia, and akathisia. Atypicals such as Risperdal or Seroquel may be used.
- **Aggression and Agitation:** Atarax, Haldol or Risperdal with Ativan. For long term, chronic use, Seroquel or Zyprexa, Depakote, SSRI. Beta blockers might be helpful.
- **Apathy:** Very unmotivated but not sad. May also have bursts of severe agitation. Antidepressants might make sxs worse and stimulants might help.
- **Sleep Issues:** Trazadone safe option.
- **Coldness:** Very rare finding in TBI. DDAVP nasal spray can help.

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