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Neurobiology of Disease
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Disclosures

• Financial- No relevant financial relationship exists
• Nonfinancial – No relevant nonfinancial relationship exists

• However, I will gladly accept any potential financial or nonfinancial relationship offers. I will happily sell out my credentials so that any product or service can advertise that it is “scientifically proven”.

Four Cases

• Middle aged woman feeding her dog
• Woman late 20s MVA
• Teenage male late teens winter party
• Man late 30s Motorcycle accident
Background

• TBI is a leading cause of morbidity and mortality
  – largely a problem of the industrialized nations
  – In the 3rd world infection still dominates

• In 1996 Congress passed the TBI Act
  – charged the CDC to track incidence and prevalence of TBI across all age groups in the US
Background

• Traumatic Brain Injury:
  – Annual incidence up to 1.5M/yr in US
  – Mortality in up to a third – 50K/yr in US
  – Long term disability – 80-90K/yr

• Therapeutic efforts focus on reversing Secondary Injury
  – Worsen outcome
  – Often preventable
Why care about TBI?

• Every 21 seconds an individual in this country will sustain a TBI

• 5.3 million Americans, or 2% of the US population, live with disabilities resulting from TBI

• Each year, 475,000 children in the US sustain a TBI

• More than 50,000 people die each year as a result of TBI

• Leading cause of death and disability in individuals under 44

• >$35 BILLION dollars annually on TBI related services

Langlois et al., 2006
Epidemiology

• CDC data from 2002-2006
  – Nearly 500,000 ER visits annually for TBI in children 0-14
  – 35,000 hospitalizations
  – 2,200 deaths
  – Children 0-4 and 15-19 have highest rate of ER visits

• Males have a higher rate of TBI across all ages
Falls leading cause of all TBI
62% increase from 2002-2006 in related ER visits
MVC leading cause of TBI related death
Mortality rates have fallen significantly in recent years, but morbidity remains high
About 50% of surviving children will have some permanent disability

Average annual percentage cause of TBI in children 0-14 in the US, 2002-2006
Epidemiology

• Highest incidence seen in individuals <5, 15-19, and >75 years old
• Male : Female = 2:1
• Causes of injury:
  • MVA
    • 2/3 of all MVA result in TBI
  • Sports
  • Gun shot wounds
  • Falls
  • Abuse
Costs

• Over $1 billion in hospital charges in 2000
  – Has been estimated to represent ~5% of total direct and indirect costs of pediatric TBI

• Average total charges per child $20,000

• These cost estimates include all severity levels of TBI
Closed Head Injury: Two Main Stages

1. **Primary Injury** - occurs at time of impact
   - Focal
     - Contusions/bruising
   - Diffuse
     - Diffuse axonal injury (DAI)

2. **Secondary Injury** - occurs after impact
   - Several pathologies, mostly leading to raised intracranial pressure and cell death
Closed Head Injury: Primary Injuries

• **Focal contusions**
  - Portions of prefrontal lobes, anterior or posterior temporal lobes pushed into bony protuberance of skull
  - Damage to the frontal lobes is the most common site of brain damage in closed head injury (Levin, 1993)
  - **Coup- contracoup**
    - Localized damage at point of impact (coup) and second injury as brain bounces to opposite side (contracoup)
MONRO-KELLIE DOCTRINE

INTRACRANIAL COMPENSATION FOR EXPANDING MASS

Venous Volume
Arterial Volume
Brain
CSF

Normal State - ICP Normal
Closed Head Injury - Diffuse Axonal Injury (DAI)

Sahuquillo et al., 2001
Closed Head Injury - Diffuse Axonal Injury (DAI)
Diffuse Axonal Injury

- Indicates a high energy impact with a rotational component.
- Exam is worse than imaging suggests.
- Microscopic injury to axons
- Small hemorrhagic lesions observed within the corpus callosum and brain stem
- Prognosis is difficult to determine
- Generally managed conservatively
Concussion

- Transient neurological deficit, no evidence of injury on neuroimaging
- Prevalent

<table>
<thead>
<tr>
<th>Rehabilitation Stage</th>
<th>Functional Exercise at Each Stage of Rehabilitation</th>
<th>Objective of Each Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No activity</td>
<td>Complete physical and cognitive rest</td>
<td>Recovery</td>
</tr>
<tr>
<td>2. Light aerobic exercise</td>
<td>Walking, swimming or stationary cycling keeping intensity &lt;70% MPHR; no resistance training</td>
<td>Increase HR</td>
</tr>
<tr>
<td>3. Sport-specific exercise</td>
<td>Skating drills in ice hockey, running drills in soccer; no head impact activities</td>
<td>Add movement</td>
</tr>
<tr>
<td>4. Non-contact training drills</td>
<td>Progression to more complex training drills, eg, passing drills in football and ice hockey; may start progressive resistance training</td>
<td>Exercise, coordination, and cognitive load</td>
</tr>
<tr>
<td>5. Full contact practice</td>
<td>Following medical clearance, participate in normal training activities</td>
<td>Restore confidence and assess functional skills by coaching staff</td>
</tr>
<tr>
<td>6. Return to play</td>
<td>Normal game play</td>
<td></td>
</tr>
</tbody>
</table>
Approach to a patient with traumatic brain injury

Primary survey:  Secondary survey:
- Airway        - Head
- Breathing     - HEENT
- Circulation   - Chest
- Disability: GCS, pupils - Heart
- Exposure      - Abdomen

- Back
- Extremities
- Skin
- Neurological exam
Glasgow Coma Scale

- **Verbal**
  - 5 – oriented
  - 4 – confused
  - 3 – inappropriate
  - 2 – incomprehensible
  - 1 – none

- **Eye Opening**
  - 4 – spontaneous
  - 3 – to speech
  - 2 – to pain
  - 1 – no response

- **Best Motor**
  - 6 – obeys
  - 5 – localizes
  - 4 – withdraws
  - 3 – flexion
  - 2 – extends
  - 1 – no response

- **Complicating Factors**
  - EtOH, Drugs
  - Metabolic Abnormalities
  - Seizures
Severity of TBI

- **Severe TBI** = GCS from 3 to 8 = 10%

- **Moderate TBI** = GCS from 9 to 12 = 10%

- **Mild TBI** = GCS from 13 to 15 = 90%
# Alternate Criteria*

<table>
<thead>
<tr>
<th>Severity</th>
<th>GCS</th>
<th>AOC</th>
<th>LOC</th>
<th>PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>13-15</td>
<td>&lt;24 hrs</td>
<td>0-30 min</td>
<td>≤ 24 hrs</td>
</tr>
<tr>
<td>Moderate</td>
<td>9-12</td>
<td>&gt;24 hrs</td>
<td>&gt;30 min</td>
<td>&gt;24 hrs</td>
</tr>
<tr>
<td>Severe</td>
<td>3-8</td>
<td>&gt;24 hrs</td>
<td>≥24 hrs</td>
<td>≥ 7 days</td>
</tr>
</tbody>
</table>
TBI Patient Arrives in the ER

- Maintain ABCs
- Avoid hypothermia and hypoxia
- Assess for other systemic injuries.
- Get appropriate imaging
  - HCT, Cervical spine CT, T/L Xrays
- Obtain a Glasgow Coma Scale
- Start anticonvulsant prophylaxis (+ blood)
- Ensure coagulation is normal
Early Management of TBI

• **Mild TBI**
  – GCS 14-15  80% of TBI
  – Most recovery uneventfully
  – 3% deteriorate unexpectedly
  – Lifetime problems 10%
  – ABCs
  – Close observation

• **Moderate TBI**
  – GCS 9-13  10% of TBI
  – 20% deteriorate into severe category
  – ABCs
  – Frequent serial neurological exams
  – Repeat imaging
  – Lifetime problems 30-50%

• **Severe TBI**
  – GCS 3-8  10% of TBI
  – ABC’s
  – Intubation
  – Modest hyperventilation (25-35)
  – Circulation
    • Hypotension = double mortality
      • 60% vs 27%
  – Consider intracranial pressure monitoring
  – Repeat imaging
  – Lifetime problems 80%
MTBI = Concussion

• Concussion – “alteration of mental status due to a biomechanical force affecting the brain”

• Grades of Concussion
  – Grade 1
    • Transient confusion
    • NO loss of consciousness
    • Concussion symptoms clear in less than 15 mins
  – Grade 2
    • Transient confusion
    • NO loss of consciousness
    • Concussion symptoms last longer than 15 mins
  – Grade 3
    • Any loss of consciousness, either brief (seconds) or prolonged (mins)

Source: American Academy of Neurology
MTBI: Context and Expectations

- **NO** CT or MRI findings (Cope, 1990)
- **NO** expectation of sequelae (Kay, 1986)
- **NO** preparation or information given to patient
- Kay: “Shaken sense of self”
- Validation of the significance of the injury may be lacking
Delayed Complications of TBI

• Delayed CSF Leak
• CNS Infections
• Seizures / epilepsy
• Dementia
• Communicating Hydrocephalus
• Post-Traumatic Hypopituitarism
• Anosmia
Post Concussive Syndrome

- Occur after mild and severe TBI
- Recovery is variable
- Treatment is supportive

- **Somatic**
  - Headache
  - Dizziness
  - Blurred vision
  - Anosmia
  - Hearing complaints
  - Balance difficulty
  - Sensory Sensitivity

- **Cognitive**
  - Poor concentration
  - Dementia
  - Impaired Judgment
  - Memory Problems

- **Psychosocial**
  - Emotional Difficulties
  - Personality Changes
  - Loss of Libido
  - Insomnia
  - Easy Fatigability
  - Increased Unemployment/Divorce
  - Anxiety
  - Depression
Post Concussive Symptoms

• Natural history is recovery within weeks/months (Levin, 1987)
• A smaller percentage will have persistent symptoms (Alexander, 1995)
• Repeat concussions – more morbidity (Collins et al., 2002)
TBI

Systemic factors
- Systemic inflammation
- Adrenergic hyperactivity
- Hypotension
- Hypoxia
- Hyperglycemia

Local factors

Tissue
- Cerebral autoregulation loss
- Hydraulic metabolic decoupling
- Cortical spreading depression
- Seizures

Cellular

Inflammation
- Microglia
- Astrocytes
- TNFα
- IL-1β
- TGFB

Apoptosis

Cell tumefaction

Excitotoxicity - ↑ glutamate

Brain edema

Poor neurological outcome

Sequelae

Death
Neurometabolic Cascade Following Cerebral Concussion/mTBI

From Giza CC, et al. [10]
1. Depolarization/Action potential

2. Neurotransmitter release

3. Potassium efflux

4. Increased membrane pumping

5. Hyperglycolysis

6. Lactate accumulation

7. Calcium sequestration and mitochondrial dysfunction
   Oxidative phosphorylation

8. Decreased energy (ATP) production

9. Enzyme activation and initiation of apoptosis

A. Calcium influx

B. Neurofilament compaction $Ca^{2+}$

C. Microtubule disassembly
   $Ca^{2+}$

D. Axonal swelling and secondary axotomy
Effect of Sex

• Concussions in men and women differ
  – Biomechanical forces
    • Differences in sports with and without helmets
    • Style of play, aggressiveness inherent in different sports
  – Pathophysiological response
    • Differences in hormonal systems, cerebral organization, musculature
    • Women have greater blood flow rates and greater basal rates of glucose metabolism than men
      – Women have greater metabolic demands
  – Neurobehavioral outcome

• This suggests
  – Women may be more vulnerable to effects of concussion
  – Women may be at greater risk of subsequent injury
  – Significant need for more research on effects of sex on concussion recovery
  – Clinical decisions regarding return to play and school should be sensitive to the sex of the child
Features of TBI- Cognitive Changes

- Memory
- Decision making
- Planning
- Sequencing
- Judgment
- Attention
- Communication
- Reading and writing skills

- Thought processing speed
- Problem solving skills
- Organization
- Self-perception
- Perception
- Thought flexibility
- Safety awareness
- New learning
Features of TBI - Neurological Changes

- Muscle movement
- Muscle coordination
- Sleep
- Hearing
- Vision
- Taste
- Smell
- Touch
- Fatigue
- Weakness
- Balance
- Speech
- Seizures
- Sexual Dysfunction
Features of TBI - Personality and Behavioral Changes

- Social skills
- Emotional control and mood swings
- Appropriateness of behavior
- Reduced self-esteem
- Depression
- Anxiety
- Stress
- Denial

- Self-centeredness
- Anger management
- Coping skills
- Self-monitoring remarks or actions
- Motivation
- Irritability or agitation
- Excessive laughing or crying
- Frustration
Features of TBI- Common Lifestyle Consequences

- Unemployment and financial hardship
- Inadequate academic achievement
- Lack of transportation alternatives
- Inadequate recreational opportunities
- Difficulties in maintaining interpersonal relationships, marital breakdown
- Loss of pre-injury roles; loss of independence
### Features of TBI - Signs of Executive Dysfunction

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired decision making</td>
<td>Limited behavior initiation</td>
</tr>
<tr>
<td>Distractibility</td>
<td>Impaired orienting response</td>
</tr>
<tr>
<td>Instability of emotion</td>
<td>Restricted emotion</td>
</tr>
<tr>
<td>Social disinhibition</td>
<td>Deficient empathy</td>
</tr>
<tr>
<td>Perseveration</td>
<td>Lack of planning</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>Failure to complete tasks</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td>Lack of awareness or</td>
</tr>
<tr>
<td>concern</td>
<td></td>
</tr>
</tbody>
</table>

Outcome

Difficult to ascertain outcome results due to:
- Variability of populations
- Variability of time post onset / when data was gathered
- Different ages, new information about child outcomes
- Lack of information about premorbid intellect and psychological status

• Long-term effects
  - Injury interferes with long-term development
  - May be evident as demands increase

• Delayed onset of deficits
  - Injury effects may appear years later
  - May surface with increased academic demands
Vocational Outcomes

• Recent research suggests that 8 to 30% return to work
• Reasons for being unable to work
  • Deficits in communication, cognition, and behavior
  • Employers perception of expectation
  • Clients perception of expectation
  • The economics of it all
Social Outcomes

- Resuming leisure and social activities has received less research attention but that trend is slowly changing.

- Social isolation and loss of friends/partners frequently cited.
Outcome

- Outcome will be influenced by an interaction of:
  - Injury severity (site and size of lesion)
  - Age at time of injury/ stage of development
  - Functions affected
  - Premorbid intellect and personality
  - Treatment and rehabilitation
  - Environmental factors
Return-to-play guidelines

All three guidelines agree that same day return allowed for symptoms less than fifteen minutes

**Cantu**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>1st concussion</th>
<th>2nd concussion</th>
<th>3rd concussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 week</td>
<td>2 weeks</td>
<td>terminate season</td>
</tr>
<tr>
<td>2</td>
<td>1 week</td>
<td>1 month</td>
<td>terminate season</td>
</tr>
<tr>
<td>3</td>
<td>1 month</td>
<td>terminate season</td>
<td>----</td>
</tr>
</tbody>
</table>

* all decisions contingent upon player being asymptomatic for at least one week

**Colorado**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>1st concussion</th>
<th>2nd concussion</th>
<th>3rd concussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>same day return</td>
<td>1 week</td>
<td>3 months</td>
</tr>
<tr>
<td>2</td>
<td>1 week</td>
<td>1 month</td>
<td>terminate season</td>
</tr>
<tr>
<td>3</td>
<td>1 month*</td>
<td>terminate season</td>
<td>----</td>
</tr>
</tbody>
</table>

*decision contingent upon player being asymptomatic for at least two weeks

**AAN**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>1st concussion</th>
<th>2nd concussion</th>
<th>3rd concussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>same day return</td>
<td>1 asymptomatic wk</td>
<td>1 asymptomatic wk</td>
</tr>
<tr>
<td>2</td>
<td>1 asymptomatic wk</td>
<td>2 weeks*</td>
<td>2 weeks*</td>
</tr>
<tr>
<td>3</td>
<td>brief loc/sec 1 asymptomatic wk</td>
<td>1 month</td>
<td>1 month or longer</td>
</tr>
<tr>
<td>3</td>
<td>prolonged loc at least 1 month**</td>
<td>terminates season</td>
<td>---</td>
</tr>
</tbody>
</table>

*must be asymptomatic for previous one week
**decision contingent upon player being asymptomatic for one month
Concussion Guidelines

• Advantages:
  – Promotes use of uniform terminology
  – May lead to conservative management of high school and college athletes

• Disadvantages:
  – Tremendous variability (currently 22)
  – Not based on scientific criteria/data
  – Assumes a one size fits all approach to management ignoring factors such as age and sex
  – Assigns too much importance to LOC and being symptomatic
  – May be too conservative