TBI Pathophysiology and Epidemiology

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Brain Injury Fellow
University of Washington

Objectives
• Able to define TBI using CDC criteria
• Able to identify:
  – the leading cause of TBI in US for ED visits, hospitalizations and deaths
• Able to describe:
  – Pathophysiology of TBI
    • Primary & Secondary
    • Focal & Diffuse

Disclosure

Pre-test
Question 1

• What is the most common cause of TBI-related ED visits, hospitalizations and deaths in United States?
  A. MVC
  B. Falls
  C. Assaults
  D. Unknown
  E. Struck by/against events

Question 2

• Overall rates of TBI presenting for ED visit is highest in which age group?
  A. 0-4 years
  B. 5-14 years
  C. 15-44 years
  D. 45-64 years
  E. 65 years and older

Question 3

• Diffuse axonal injury is classically seen in following structures except:
  A. Corpus callosum
  B. Central white matter
  C. Basal ganglia
  D. Corona radiata
  E. Cerebellum
TBI: Definition

- Reasonable mechanism
- Subjective/objective report
- Imaging findings

Injury to the head

- Subjective report
- Objective report

Loss / Decreased level of consciousness

- Data collection

Objective Neuro/psych findings

http://www.cdc.gov/ncipc/pub-res/tbi_congress/05_references_appendix.htm

Diagnose TBI

- Clinical diagnosis
  1. Reasonable mechanism of injury
  2. LOC / dazed / amnesia at the time of injury
  3. Objective neuro/psychological abnormalities

- Differentiate from whiplash

http://www.cdc.gov/ncipc/pub-res/tbi_congress/05_references_appendix.htm

Diagnose TBI

- Reasonable mechanism of injury
  A. Blunt trauma
  B. Penetrating trauma
  C. Acceleration / deceleration
    - MVC
    - Collision (sports, transportation injuries)
  D. Blast

http://www.cdc.gov/ncipc/pub-res/tbi_congress/05_references_appendix.htm
Neuro Assessment

- Objective neuro/psychological abnormalities
- History and observation **acutely following trauma**
- Examples:
  - Motor function
  - Sensory function
  - Reflexes
  - Abnormalities of speech
  - Seizures

Psych/Behavior Assessment

- Objective neuro/psychological abnormalities
- Mental status exam
- Neuropsychology exam
- Examples:
  - Disorders of mental status
    - Disorientation, agitation, confusion
  - Other changes in cognition, behavior or personality

TBI Epidemiology

- All numbers are from CDC TBI data
- Divided into:
  - ED visits
  - Hospitalizations
  - Deaths
- Age divided into: 0-4, 5-14, 15-24, 25-44, 45-64, 65 and older
- [http://www.cdc.gov/traumaticbraininjury/data/](http://www.cdc.gov/traumaticbraininjury/data/)
Epidemiology

• Overall **2.5 million** emergency department visits, hospitalizations, or deaths were associated with TBI in the US (2010)
  – Contributed to **death** of more than 50,000 people
  – Diagnosis in more than 280,000 **hospitalizations** and **2.2 million ED visits**

Epidemiology from 2001-2010

• Rates of TBI-related **ED visits**:  
  – Increased by 70%
• Rates of TBI-related **hospitalizations**:  
  – Increased by 11%
• **Death** rates related to TBI:  
  – Decreased by 7%

Definition

• **Cause of injury**: a description followed by the CDC that would allow for public health tracking and interventions  
  – e.g.) assault, falls, MVC
• **Mechanism of injury**: description used medically to help us describe to each other the type(s) of external forces that were exerted on the brain  
  – e.g.) blunt force trauma, sharp force trauma (penetrating), acceleration/deceleration forces, blast
Epidemiology: Causes (Fall)

- From 2006-2010, falls were the leading cause of all TBI
  - 40% of all TBIs in the US that resulted in ED visit, hospitalization, or death
- Falls disproportionately affect the **youngest and oldest age groups**
  - 55% of TBIs among children (0-14)
  - 81% of TBIs in adults aged 65 and older

Epidemiology: Causes (blunt trauma)

- Unintentional blunt trauma is the second leading cause of overall TBI
  - 15% of all TBIs in the US from 2006-2010
  - 24% of all TBIs in children less than 15

Epidemiology: Causes (MVC)

- In all age groups, 3rd leading cause of all TBI was **MVC** (14%)
- TBI-related **deaths**:
  - MVC: the **second leading** cause (2006-2010)
Epidemiology: Deaths

- Men are 3 times likely to die as women

- Highest rate: 65 years and older
- Leading cause of death varied by age
  - For 65 and older: Falls
  - For children and young adults (5-24): MVC
  - For children (0-4): assaults

Epidemiology: non-fatal TBI (ED)

- Men had higher rates for hospitalization and ED visits
- ED visit rates highest among children (0-4)
- Leading cause of ED visits:
  - Falls in all age group except for 15-24 age group (assaults)
Epidemiology

- From 2001 to 2009, the rate of ED visits for sports and recreation-related injuries with a diagnosis of concussion or TBI rose 57% among children (age 19 or younger)

Epidemiology: non-fatal TBI (hospitalization)

- Hospitalization rates highest among 65 and older
- Leading causes of hospitalization varied by age:
  - For children 0-14 and adults 45 and older: falls
  - For ages 15-44: MVC

Epidemiology: Severity

- Mild: 80%
- Moderate: 10%
- Severe: 10%
Epidemiology

- 40% of people hospitalized with TBI report at least one ongoing issue at one year after
- At least 5.3 million Americans have a need for long-term or lifelong assistance with ADLs from TBI
- Direct medical and indirect lost productivity costs estimated at $60 billion in 2000

Epidemiology: Military

- 30% of service members evacuated between 2003 and 2005 had sustained a TBI
- Leading causes:
  - Blast injury 72%
  - Falls 11%
  - Vehicular incidents 6%
  - Injuries caused by fragments 5%
  - Other injuries 6%

Key points: Epidemiology

- FALLS were the leading cause for overall TBI in 2006-2010
  - Disproportionally affect the youngest (0-14 years) and oldest age groups (65 and older)
- Unintentional blunt trauma was the second most common cause for overall
- Assaults was the least common mechanism overall

Key points: Epidemiology

- Over the past decade (2001-2010), while rates of TBI-related ED visits increased by 70%, hospitalization rates only increased by 11% and death rates decreased by 7%
- Leading cause of TBI-related deaths varied by age:
  - Assault: 0-4 years
  - Motor vehicle crash: 5-24 years
  - Fall: 65 years and older
TBI Pathophysiology

Definition
- **Cause of injury**: a description followed by the CD that would allow for public health tracking and interventions
- **Mechanism of injury**: description used medically to help us describe to each other the type(s) of external forces that were exerted on the brain
- **Pathophysiology of injury**: description of the injury that is seen in the brain from the sub-cellular to gross anatomy range

Pathological Injury Classification

- **Anatomical**:
  - Focal
  - Diffuse
- **Pathophysiological**:
  - Primary
  - Secondary

- **Mechanistic**:
  - Impact
  - Inertial loading
  - Penetrating
  - Blast

Pathological Injury Classification

<table>
<thead>
<tr>
<th>Primary Brain Injury</th>
<th>Diffuse Brain Injury</th>
</tr>
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<tbody>
<tr>
<td>- Focal cortical contusion</td>
<td></td>
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<tr>
<td>- Intracerebral hemorrhage</td>
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<tr>
<td>- Extracerebral hemorrhage</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Brain Injury</th>
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<tbody>
<tr>
<td>- Delayed neuronal injury</td>
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<tr>
<td>- Diffuse brain swelling</td>
<td></td>
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<tr>
<td>- Diffuse ischemic injury</td>
<td></td>
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<tr>
<td>- Diffuse hypoxic injury</td>
<td></td>
</tr>
<tr>
<td>- Diffuse metabolic dysfunction</td>
<td></td>
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Pathophysiology

• **Primary injury**
  – Injury at the moment of impact
  – Caused by displacement of physical structures

• **Secondary injury**
  – Injury through biochemical cascades
  – Impacts of biochemical cascade may be visualized more grossly, such as in diffuse cerebral edema

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Primary Injury

• Contusion
• Force at the site of the impact or the opposite the impact (Coup-Contrecoup)
• Diffuse axonal injury (DAI)
• Metabolic factors (impact depolarization)
• Vascular injury
• Blast

Primary Injury

• Contusion:
  – *Bruising* of the surface of the brain
  – Classically involve **frontal** and **temporal** lobes
Primary Injury

- **Coup-Contrecoup**
  - Contusion located in **diametrically opposite** ends
  - Usually involving **frontal (coup)** and **occipital (contrecoup)** lobes

**Primary Injury**

- **Diffuse Axonal Injury**
  - Classically affects **white matter** in areas including **corpus callosum, basal ganglia, thalamus, cerebral hemispheres, and brainstem**
  - Considered to be an important cause of **severe disability** and **vegetative state** in survivors
    - Severe disability is possible with normal CT
Primary Injury: DAI

- Affects the brain on macroscopic and microscopic level
  - Macro: Hemorrhage from tearing of blood vessels
  - Micro: Increases cell membrane permeability

Primary Injury

- Impact depolarization
  - Physical force leading to glutamate release (excitatory)
    - leads to excitotoxicity (secondary injury)
    - Even in mild TBI

**Primary Injury: DAI**

- Thought to be from modified focal axonal sections leading to disruption of axonal transport impairment and axonal swelling, followed by detachment over a period of time
Focal Injury

Pathological Injury Classification

- Anatomical:
  - Focal
  - Diffuse
- Pathophysiological:
  - Primary
  - Secondary
- Mechanistic:
  - Impact
  - Inertial loading
  - Penetrating
  - Blast

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<td></td>
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</tr>
<tr>
<td></td>
<td>- Diffuse metabolic dysfunction</td>
<td>- Regional metabolic dysfunction</td>
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Focal Injury

- Epidural hematoma (EDH): most commonly associated with fracture
- Subdural hematoma (SDH): most common seen after head injury, up to 5% of all head injuries
- Subarachnoid hemorrhage (SAH): primary traumatic SAH has high mortality
**Key Points: Primary Injury**

- **Contusion**: bruising of the cortical tissue
  - Classically at inferior frontal lobe and anterior temporal lobe
- **Diffuse axonal injury (DAI):**
  - Disruption of axons from acceleration/deceleration forces
  - Classically seen at corpus callosum, central white matter, midbrain, and the cerebral hemispheres
  - Visualized as white matter petechial hemorrhages
Secondary Injury

- Cascade of biochemical, cellular, and molecular events that occurs **hours to days** after the initial impact
- Mechanisms include:
  - Ischemia
  - Secondary cerebral swelling
  - Axonal injury
  - Inflammation

Secondary Injury: Metabolic Cascade

- Physical trauma disrupts cell membrane integrity
- Rapid shift of Na+ and Cl- results in:
  - An influx of calcium ions into the cell
  - Calcium triggers a proteolysis of cytoskeletal structure
  - Cell injury and apoptosis
Secondary Injury: Metabolic Cascade

- Burst of excitatory molecules
- Release of oxygen free radicals
- Inflammation / Arachidonic acid cascade
- Loss of blood brain barrier

All of which results in: **Increased metabolic demands**

Secondary Injury: Ischemia

- Diffuse ischemic injury secondary to:
  - Increasing cerebral swelling
  - Cardiorespiratory arrest
  - Profound hypotension from other injuries
- **Lactate accumulation** secondary to the absence of blood flow leads to cellular damage

Secondary Injury: Swelling

- Hallmark finding in **severe** TBI, leading to increased ICP
  - Compromise cerebral perfusion
  - Herniation

Neurotransmitter Dysfunction

Neurotransmitter Dysfunction

- Acute alterations of cerebral neurotransmitter levels seen after the injury possibly from stretching and straining forces to the brain
- Excess neurotransmitter ("neurotransmitter storm") is thought to contribute to the early neuropathophysiology of TBI

Why care about neurotransmitters?

- Glutamate: mediator of excitatory signals for normal brain function
- Dopamine: motor movement, mood, and possibly arousal
- Norepinephrine: attention
- Serotonin: cognitive function & stabilizing and modulating brain function as well as mood
  - Most disrupted by DAI
- Acetylcholine: memory & motor function

Glutamate

- Elevated within minutes and peak over the first 48 hrs
- Principal neurotoxic effect is attributable to excess activation of NMDA receptor
- Also drives glucose utilization past brain's capacity, resulting in toxic accumulations of lactate

Catecholamines

- Epinephrine
- Norepinephrine
- Dopamine
Catecholamines

- Intracerebral level increased in immediate post-injury period
  - Persistent elevation of dopamine and norepinephrine are inconsistently associated with poor outcome
- May contribute to post-traumatic cognitive and other neuropsychiatric disturbances

Serotonin

- Serotonergic efferents are particularly vulnerable to secondary neurotoxicity
- In humans, ventricular CSF sampling shows increased serotonin in immediate post-injury period
- Level may differ in focal vs diffuse injury
  - Decreased in focal frontotemporal contusion
  - Increased with diffuse injuries

Acetylcholine

- Elevated in immediate post-injury period
- Contribute to acute alterations of arousal
- There may be early post-injury cholinergic excess followed by development of late cerebral cholinergic deficits

Questions
Question 1

- What is the most common cause of TBI-related ED visits, hospitalizations and deaths in United States?
  A. MVC
  B. Falls
  C. Assaults
  D. Unknown
  E. Struck by/against events

Answer 1

- Leading Causes of TBI
  - Falls, 40.5%
  - Motor vehicle traffic, 14.3%
  - Strikes by or against, 15.9%
  - Assaults, 18.7%
  - Unknown Other, 16.0%

Question 2

- Overall rates of TBI presenting for ED visit is highest in which age group?
  A. 0-4 years
  B. 5-14 years
  C. 15-44 years
  D. 45-64 years
  E. 65 years and older

Answer 2

- Rates of TBI related Emergency Department Visits by Age Group
  - United States, 2001-2010
  - Graph showing increasing trend from 2001-2010 for different age groups.
Question 3

- Diffuse axonal injury is classically seen in following structures except:
  A. Corpus callosum
  B. Central white matter
  C. Basal ganglia
  D. Corona radiata
  E. Cerebellum

Primary Injury

- Diffuse Axonal Injury
  - Classically affects white matter in areas including corpus callosum, basal ganglia, thalamus, cerebral hemispheres, and brainstem

Reference


Supplemental info

• Centripetal Injury aka DAI
  – Grade 1
    • Histologic evidence of axonal damage
    • No focal injury on imaging
  – Grade 2
    • Imaging indicates a focal lesion in corpus callosum
  – Grade 3
    • Brainstem lesion on imaging

Learning Objectives - 1

- Define TBI severity using GCS and PTA
- Describe functional prognosis after moderate to severe TBI using trends and threshold values

Learning Objectives - 2

- List key parameters of:
  - Glasgow Coma Scale (GCS)
  - Disability Rating Scale (DRS)
  - Galveston Orientation & Amnesia Test (GOAT)
  - Level of Cognitive Functioning Scale (Rancho)

Clinical Diagnosis of TBI
Diagnose TBI – **clinical diagnosis**

1) Reasonable mechanism of injury
2) LOC / Dazed / Amnesia at the time of injury
3) Objective neuro/psychological abnormalities
   → Differentiate from whiplash

“...To plunge or not to plunge, that was the question!...I had plunged, throwing out my arms to embrace the summit of the fir tree...It was 3 days before I regained consciousness and more than 3 months before I crawled from my bed.

The measured fall was 29 feet on to hard ground. Later on when I could understand again...I had among other injuries a ruptured kidney.”

Q: Who’s describing their severe TBI?

1) Bob Woodruf  
2) Richard Hammond  
3) Winston Churchill  
4) Abraham Lincoln

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**Case**

- Mr. TBI is a 25yo office manager who was in a MVC 2 weeks ago...  
  - Speed was 45mph  
  - LOC 5 minutes  
  - Initial head CT with right frontal IPH, left occipital small SDH, diffuse petechial hemorrhage  
  - Reports dizziness, headaches, irritability, sleep changes, and cognitive impairment
TBI Severity

• Who cares?
  – People who write tests
  – Clinical correlations
  – Correct diagnosis
    • Fixed in time
  – Research starting to define interventions for different groups
  – Generalizing the literature

• Options for severity classification
  – Clinical
    • Glasgow coma scale (GCS)
    • Duration of post-traumatic amnesia (PTA)
    • Concussion (mild TBI) grading scales (out of favor)
  – Radiographic
    • Marshall CT classification
    • Rotterdam CT classification

TBI Severity

• Timing of Assessment

• Timeframe variable in the literature
  – Clinically conservative: use more severe indicator
  – Be careful about generalizing the literature
** TBI Severity Using GCS **

- **Mild:** 13-15
  - Mild-complicated: 13-15 with CT or MRI findings

- **Moderate:** 9-12

- **Severe:** 3-8 = Coma
  - Intubate...

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** TBI Severity Using PTA **

<table>
<thead>
<tr>
<th>Duration of PTA</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 minutes</td>
<td>Very mild</td>
</tr>
<tr>
<td>5-60 minutes</td>
<td>Mild</td>
</tr>
<tr>
<td>1-24 hours</td>
<td>Moderate</td>
</tr>
<tr>
<td>1-7 days</td>
<td>Severe</td>
</tr>
<tr>
<td>1-4 weeks</td>
<td>Very severe</td>
</tr>
<tr>
<td>&gt; 4 weeks</td>
<td>Extremely severe</td>
</tr>
</tbody>
</table>

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** GOAT **

- Assess both remote memories, time of injury memories, and post-injury memories

- PTA ends when GOAT scores are greater than 75 for two consecutive trials, 24 hours apart
Case

• Mr. TBI is a 25yo office manager who was in a MVC 2 weeks ago...
  – Speed was 45mph
  – LOC 5 minutes
  – Initial head CT with right frontal IPH, left occipital small SDH, diffuse petechial hemorrhage
  – Reports dizziness, headaches, irritability, sleep changes, and cognitive impairment

Case - Diagnosis

• Did Mr. TBI have a TBI?
  ✓ Mechanism of injury
  ✓ Change in consciousness
  ✓ Neuro/psych/behavioral symptoms and signs

Q: After resuscitation Mr. TBI has responses of:
  - Opens eyes to pain
  - Mumbles incomprehensible words
  - Withdraws from pain
  What's his GCS score?

1) 8  
2) 9  
3) 11  
4) 13

Q: After resuscitation Mr. TBI has responses of:
  - Opens eyes to pain
  - Mumbles incomprehensible words
  - Withdraws from pain
  How severe is his TBI?

1) Mild  
2) Mild-complicated  
3) Moderate  
4) Severe
Mr. TBI’s GOAT score today is 78, yesterday’s score was 73. Is Mr. TBI out of PTA?

1) Yes
2) No

Radiographic classifications

Marshall CT (computed tomography) classification of traumatic brain injury

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse injury I (no visible pathology)</td>
<td>No visible intracranial pathology seen on CT scan</td>
</tr>
<tr>
<td>Diffuse injury II</td>
<td>Cerebrospinal fluid shift of 3–5 mm and/or lesions denser than gray matter</td>
</tr>
<tr>
<td>Diffuse injury III (cavitary)</td>
<td>Lesions greater than 5 mm in diameter</td>
</tr>
<tr>
<td>Diffuse injury IV (SIH)</td>
<td>Lesions greater than 5 mm in diameter, no high- or mixed-density lesion</td>
</tr>
<tr>
<td>Evacuated mass lesion I</td>
<td>Any lesion surgically evacuated</td>
</tr>
<tr>
<td>Non-evacuated mass lesion II</td>
<td>High- or mixed-density lesion &gt;2.5 cm^2, not surgically evacuated</td>
</tr>
</tbody>
</table>


Rotterdam CT (computed tomography) classification of traumatic brain injury

<table>
<thead>
<tr>
<th>Predictor value</th>
<th>Score</th>
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<tbody>
<tr>
<td>Basal clefts</td>
<td></td>
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<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Compressed</td>
<td>1</td>
</tr>
<tr>
<td>absent</td>
<td>2</td>
</tr>
<tr>
<td>Midsagittal shift</td>
<td></td>
</tr>
<tr>
<td>No shift or shift &gt;5 mm</td>
<td>0</td>
</tr>
<tr>
<td>Shift &gt;1 cm</td>
<td>1</td>
</tr>
<tr>
<td>Epidural mass lesion</td>
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<tr>
<td>Present</td>
<td>0</td>
</tr>
<tr>
<td>absent</td>
<td>1</td>
</tr>
<tr>
<td>Intraventricular blood or subarachnoid hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>San score</td>
<td>Total = 5</td>
</tr>
</tbody>
</table>

Using Severity to Predict Stuff

Non-penetrating Moderate to severe TBI...

TBI Outcome Studies → GOS
- 1 = DEATH
- 2 = VEGETATIVE STATE
  Unable to interact with environment; unresponsive
- 3 = SEVERE DISABILITY
  Able to follow commands/ unable to live independently
- 4 = MODERATE DISABILITY
  Able to live independently; unable to return to work or school
- 5 = GOOD RECOVERY
  Able to return to work or school

http://www.tbims.org/combi/gos/index.html

Mortality / Vegetative

Jennet (1979)
- GCS 3-4: death or vegetative in 87%
- GCS 5-7: death of vegetative in 53%

McMillan (2011) and other cohort studies
- 30% mortality in severe TBI
- Increased mortality 13 years post injury

Disorders of Consciousness

<table>
<thead>
<tr>
<th>Sleep Cycles</th>
<th>Eye Opening</th>
<th>Follow Commands</th>
</tr>
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<tr>
<td>Coma</td>
<td></td>
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<td>Vegetative State</td>
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Mod-Severe TBI: Risk Factors

- Lower GCS
- Longer duration of coma
- Longer PTA
- Older age
- Deeper lesions on imaging
- Fixed pupils
- Associated injuries
- Hypotension
- Hypoxia
- Pyrexia
- Elevated ICP
- Bleeding issues

Functional Prognosis Mod-Severe TBI

- **Threshold values** → what’s *unlikely* to happen
  - **Severe disability unlikely**
    - Time to follow commands less than 2 weeks
    - Duration of PTA less than 2 months
  - **Good recovery unlikely**
    - Time to follow commands more than 4 weeks
    - Duration of PTA more than 3 months
    - 65+ years old
    - Bilateral brainstem lesions on MRI within 2 weeks

Q: A patient had 9 days of post-traumatic amnesia after severe TBI. What can you confidently say about this functional prognosis?

1) Severe disability likely
2) Severe disability unlikely
3) Good recovery likely
4) Good recovery unlikely
Assessment Scales
...make good test questions

Key Scales Available...

Disability Rating Scale (DRS)

Q: How many items categories are on the DRS?

1) 8
2) 18
3) 38
4) 80
Q: A score of 29 on the DRS reflects:

1) No disability
2) Mild confusion
3) Moderate disability
4) Extreme vegetative state

Disability Rating Scale (DRS)

• “From coma to community”
  – Less helpful reflecting recovery course in mTBI
• Score 0-29
  • 0 = no disability

http://www.tbims.org/combi/drs/index.html

Level of Cognitive Functioning Scale

...aka the Rancho

Q: After TBI a patient is described as displaying bizarre, nonpurposeful, incoherent or inappropriate behaviors, has no short-term recall, attention is short and nonselective.

1) 1  5) 5
2) 2  6) 6
3) 3  7) 7
4) 4  8) 8
Level of Cognitive Functioning Scale

I - No response
II - Generalized
III - Localized
IV - Confused-agitated
V - Confused, inappropriate, non-agitated
VI - Confused-appropriate
VII - Automatic-appropriate
VIII - Purposeful-appropriate

http://www.tbims.org/combi/lcfs/lcfs.pdf
http://www.rancho.org/research_rancholevels.aspx

Practice the Rancho...

Q: After TBI a patient is described as reacting to external stimuli in nonspecific, inconsistent, and nonpurposeful manner with stereotypic and limited responses.

1) 1 5) 5
2) 2 6) 6
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Q: After TBI a patient is described as: Oriented and responds to the environment but abstract reasoning abilities are decreased relative to premorbid levels.

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Q: After TBI a patient is described as displaying random, fragmented, and nonpurposeful responses to complex or unstructured stimuli.

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References and Readings

References and Readings


COAT


The Children’s Orientation and Amnesia Test (COAT) was developed for assessing cognition serially during the early stage of recovery from moderate or severe head injury in children and adolescents. The score for the COAT, which is composed of 14 items evaluating general orientation, temporal orientation, and memory, were derived from data obtained from 56 children aged 7 to 15 years, 27 patients with head injuries, the duration of post-traumatic amnesia, as indicated by the duration of day (DOT). Scores were in the 30-60 range for children with moderate head injuries, decreasing to the 50-10 range for severe head injuries. Children with severe head injury had a shorter duration of post-traumatic amnesia than the Glasgow Coma Scale score at 6 and 12 months after the injury. This study showed that the COAT has adequate reliability and validity as a measure of the duration and severity of posttraumatic amnesia in children and adolescents.
Mild TBI
Classic Symptoms & Approach to Treatment

Jennifer M Zumsteg, MD
March 2015

Disclosures
• none

Learning Objectives
• Review concussion and mild TBI for clinical diagnosis
• Utilize literature to predict course and outcome
• Manage common symptoms and syndromes after mild TBI
• Compare sports-related and military concussion

Definitions and prevalence of mTBI / Concussion
True or False...

- All mTBIs are concussions
- All concussions are mTBIs

mTBI

- All mTBIs are concussions
- All concussions are mTBIs

Middle English concussioun, from Latin concussion-, concussio, from concutere
to shake violently, from com- + quaterē to shake

Concussions are Funny
Concussions are NOT Funny

TBI severity Symptom Severity

Concussion Management Plan?

Our Agenda...

• MTBI/concussion – definitions
• Pathophysiology
• Early symptoms and prognosis in MTBI/Concussion
• Diagnosis and testing for MTBI/concussion
• Post-concussion persisting symptoms
• Sports-related concussion
• Blast-related concussion
• Management of MTBI

Realms of Mild TBI

• Sports Concussion
• Overall mTBI

Return to play

BROAD management
Realms of Mild TBI

- Sports Concussion
- Overall mTBI

Different Research

Return to play

BROAD management

CDC Operational (Clinical) Mild TBI Definition

- Any period of observed or self-reported
  - Transient confusion, disorientation, impaired consciousness
  - Amnesia
    - Post-traumatic amnesia less than 24 hours
    - LOC 30 minutes or less


CDC Mild TBI Definition

- Observed signs of neurologic/neuropsychological dysfunction
  - Seizures
  - Irritability, lethargy, vomiting in infants/young children
  - Symptoms identified soon after injury in older children/ adults such as
    - Headaches, dizziness, irritability, fatigue, poor concentration
    - Symptoms cannot be used to make diagnosis in absence of LOC or altered consciousness

It’s worse than mTBI when...

- LOC greater than 30 minutes
- PTA greater than 24 hours
- Initial GCS ≤ 12
- Cranial nerve injuries
- Findings on head CT or MRI

- Concussion sub-rating scales of severity - limited use
OEF/OIF Experience

- 10% of 7,909 Marines with the 1st Marine Division suffered brain injuries. Researchers tried to follow up with 500 Marines who suffered concussions. They reached 161 of them and found that 83% were still suffering symptoms on average 10 months after the injury. USA Today 6/8/06
- Between 10 and 30% deployed service members have had TBI (Elder and Cristian, Mt Sinai J Med, 2009; Tanielian and Jaycox, RAND, 2008; Meyer et al., J Trauma Nursing 2008).

Pathophysiology and Diagnosis of MTBI/Concussion

Acute Metabolic Cascade

- Physical trauma causes a loss of cell membrane integrity
- A rapid shift of cations and anions results in:
  - Burst of excitatory molecules
  - Calcium triggers a proteolysis of cytoskeletal structure
  - Cell injury and apoptosis

Acute Metabolic Cascade

- Cell membrane and axonal stretching
  - Ionic disequilibrium – spreading excitation and depression
    - ↑K⁺ and glutamate release
    - Activation NMDA receptors and ↑intracellular Ca²⁺
    - Mitochondrial dysfunction, protease activation, apoptosis
- Cerebral blood flow-glucose metabolism uncoupling
Other Causes of Secondary Injury

- Release of oxygen free radicals
- Inflammation / Arachidonic acid cascade
- Loss of blood brain barrier integrity

• All of which results in:
  - Increased metabolic demands

Mismatch between blood flow and metabolic demand

Potential longer term effects

- Experimental models: brain activation altered for several weeks after even MTBI
  - Potential diffuse axonal injury
  - Alterations in synaptic plasticity and axonal sprouting
  - Neurotransmitter alterations
  - Hypothalamic pituitary adrenal axis dysregulation

Concussion is still a clinical diagnosis

- Primary role of neuroimaging: exclude a more severe injury or mass lesion
  - CT scan: insensitive to MTBI - rules out presence of hemorrhage
  - When to image: Clinical decision
**American Social of Neuroradiology**

- “Advanced” imaging still for research
- Very difficult to apply clinically
- Stay tuned...

**Neuropsychological Assessment**

- Most convincing if baseline data exists as comparison points
  - Athletics may have baseline data
    - ImPACT – Immediate Post Concussion Assessment and Cognitive Testing...
      - adult norms not clearly available
  - Baseline school data may be helpful
  - Structured interview helpful

**Neuropsychological Assessment Testing Options**

- Computerized: volume, cost, alternate tests
  - no info on auditory processing or verbal memory, no recall memory, no observation

- Board Certified Neuropsychologist:
  - Higher cost, more time, **gold standard**

**Classic Profile of MTBI:**

- Slowed mental processing time
- Impaired complex memory
- Impaired complex attention
When to Refer for NPE

- Individualized, goal directed
- Education level and Language
  - Same primary language, 6th grade education
- Reasonable functional plateau
- Tolerate testing
- Minimize interference factors
  - Mood, pain, sleep, motor impairments, meds

Symptoms and Recovery after Concussion/Mild TBI

Post-traumatic Symptoms

- The majority of patients with mild TBI will have no symptoms within several weeks
- Early reassurance and education in mTBI helps with recovery

Language, Connotation, Expectation

- Post-traumatic symptoms
  - What’s expected after mTBI?
  - What’s expected after severe TBI?
- Post-concussion syndrome
  - What does your gut say...?
Post-Concussive Syndrome (ICD10)

• A. History of head trauma with loss of consciousness preceding symptom onset by a maximum of 4 wk.

• B. Symptoms in 3 or more of the following symptom categories:
  • headache, dizziness, malaise, fatigue, noise intolerance;
  • irritability, depression, anxiety, emotional lability;
  • subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment;
  • insomnia;
  • reduced alcohol tolerance; and
  • preoccupation with above symptoms and fear of brain damage with hypochondriacal concern and adoption of sick role.

Post-Concussive Syndrome (DSM)

• (A) history of TBI causing "significant cerebral concussion"
• (B) objective cognitive deficit in attention and/or memory
• (C) presence of at least 3 of 8 symptoms (fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, personality change, apathy) that appear after injury and persist for 3 months
• (D) symptoms that begin or worsen after injury
• (E) interference with social role functioning
• (F) exclusion of dementia due to head trauma and other disorders that better account for the symptoms.

Clinical practice guidelines for mild traumatic brain injury and persistent symptoms

Abstract

Objective To outline new guidelines for the management of mild traumatic brain injury (MTBI) and persistent post-concussive symptoms (PPCS) in order to provide information and direction to physicians managing patients' recovery from MTBI.

Quality of evidence A search for existing clinical practice guidelines addressing MTBI and a systematic review of the literature evaluating treatment of PPCS were conducted. Because little guidance on the management of PPCS was found within the traumatic brain injury field, a second search was completed for clinical practice guidelines and systematic reviews that addressed management of these common symptoms in the general population. Health care professionals representing a range of disciplines from across Canada and abroad were brought together at an expert consensus conference to review the existing guidelines and evidence and to attempt to develop a comprehensive guideline for the management of MTBI and PPCS.

Conclusions Based on these recommendations, this guideline is intended to provide a comprehensive set of clinical recommendations to address the diagnosis and management of MTBI and PPCS. In addition, numerous resources and tools were included in the guideline to aid in the implementation of the recommendations.

Conclusion A clinical practice guideline was developed to aid health care professionals in implementing evidence-based, best practice care for the challenging population of individuals who experienced PPCS following MTBI.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3300645/

Back to symptoms...
Post-traumatic Symptoms

- Symptoms persist after a Mild TBI at a rate of 5 to 20% at one year.

- Patients referred to a brain injury clinic months to years after injury have high rates of chronic pain and other symptoms.

Chronic Pain in Chronic Mild TBI

Frequency of Concurrent Chronic Pain Problems

- Symptoms are measured by patient report
  - Patients may over-report incidence and severity of symptoms
  - Patients may attribute all problems as caused by the mild TBI
  - Consider baseline...There can be a relatively surprisingly high rate of problems such as headaches in control subjects without a TBI
Persistent Post-traumatic Symptoms

- Ponsford study
  - 84 subjects with mild TBI in ED
  - At 1 week sign. increases headaches, dizziness, fatigue, visual, memory problems
  - Sign. Diff. on NP tests

Risk Factors for Persisting Symptoms

- Previous concussion or other brain disorder
- Severity of Injury
- Stress related disorder (PTSD, anxiety)
- Expectations
- Depression
- “All or nothing” personality
- (Gender, legal)

Conclusions

- Large number of concussions/MTBI
- Diagnosis may be difficult
  - Need credible mechanism of injury
  - Symptoms do not make diagnosis
- Most people recover with no symptoms
- Difficult to predict who will have persistent symptoms
- Treatment options – prevent problems or wait to treat problems?

References:
Sports Related Concussions

- CDC Estimates of incidence
  - 1.6 to 3.8 million sports-related concussions annually
  - 135,000 evaluated in ED annually

- Each concussion increases the likelihood of sustaining another concussion

- Why are concussions increasing?
  - Change in awareness and diagnosis
  - Change in the game
    - Football – bigger players, more wide-open game
    - Baseball – bat composition
    - More women involved in competitive levels of team sports
    - Equipment changes that increase speed (bicycles, skis)
**On the Field Evaluation of Concussion**

- Exclude cervical spine injury
- Remove the athlete from play
- Assess the injury using a standard procedure (SCAT2 – signs or symptoms, memory questions, balance)
  - Evaluate cognitive status (e.g., SAC)
  - http://www.cdc.gov/concussion/HeadsUp/clinicians/resource_center/assessments_tools.html
- Monitor the athlete over the next 4-6 hours
- No return to play the day of injury
- No driving home from event
- (No alcohol)

**Further Assessment**

- No return to play same day – ALL levels
  - Prevent second impact; allow assessment
- Evaluation by medical professional prior to Return to Play
  - Children: RTP law in all 50 states
- When to CT scan
  - Prolonged disturbance of consciousness, worsening symptoms, focal neurological status, seizure

**Return to Play – minimum 5-7 days**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Protocol/Exercise</th>
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<td>No activity</td>
<td>Physical/cognitive rest</td>
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<td>Light aerobic exercise</td>
<td>Walking/swimming/stationary bicycle &lt;70% max HR No resistance training.</td>
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<tr>
<td>Sport specific exercise</td>
<td>No head impact activities</td>
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<tr>
<td>Non contact training drills</td>
<td>Increase complexity and cognitive load. Resistance training</td>
</tr>
<tr>
<td>Full contact practice</td>
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<tr>
<td>Return to play</td>
<td>Normal game activities</td>
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**Chronic traumatic encephalopathy**

- Boxing 1928: “punch-drunk” (dementia pugilistica)
  - Risk factors: boxing as teenagers, >10 year career, number of matches, ApoE4 allele
  - To date, imaging not helpful in predicting
- Current concerns: chronic concerns for brain and spinal cord damage (neurofibrillary materials/tau protein) in a relatively small number of athletes
  - Prominent mood disorders
Prevention
- Use of helmets in sports where there is danger of head trauma
- Use of guidelines for RTP
- Reduction of intentional head (helmet) contact
- Strengthening
- Equipment changes

MTBI and Blast Exposure
- Mechanisms for brain injury
  - Primary injury: blast pressure waves (size of wave, distance from blast, reflection waves) – affect eyes, ears, lungs, brain
  - Secondary injury: flying debris (penetrating or blunt injuries)
  - Tertiary Injury: person being tossed by pressure wave (fractures, traumatic amputations, brain injury)
  - Quarternary Injury: Other including exacerbation of existing injury

Complications of Blast Related TBI
- Presence of amputations, blindness, hearing loss, burns, musculoskeletal injury
- Co-existence with acute and post-traumatic stress disorders

Rehabilitation Treatment of Individuals with Mild TBI and Persistent Symptoms
Key Principles of Treatment

• Validate the experience of the person (impairment and subjective complaints)
• Do not assume psychological factors as the primary problem and source of disability
• Incorporate successful functional tasks into therapy program to allow patient to re-build sense of control

Key Principles of Treatment

• Treat physical, psychological, and cognitive problems
• Address the complaints with concrete action
• Begin the process of sorting out primary problems (physical or cognitive) from secondary (psychological) problems

Medical Treatment

• Psychological Problems
  – Depression and anxiety
  – Sleep Disturbance
  – Anger management
• Headache
• Pain, neck and back
• Dizziness, vestibular dysfunction

Headache after TBI

• Post-traumatic headache (PTH) is one of the most common persisting symptoms after injury, with prevalence ranging from 30-90% of patients in studies to date. PTH occurs more commonly in those with lesser severity brain injury.
  – Ioh & Bryant, 1996
• PTH is the salient physical symptom after blast exposure in military populations.
  – Hoge et al., 2008; Theeler & Erickson, 2009
• PTH can be chronic, with 18-22% persisting past one year.
  – Ioh et al., 2006
• Patients with PTH reported greater functional impairment than those with non-traumatic headache.
  – Marcus, 2003
• Athletes with headaches following concussion performed worse on cognitive testing than those without.
  – Mihalik et al., 2005
• ICH criteria do not contribute to treatment planning and do not account for latency of PTH following trauma.
  – Theeler & Erickson, 2009

**Post-traumatic Headaches**

By definition → start within 7 days

http://ihs-classification.org/en/

**Sample:**

**Acute Post-Traumatic Headache**

- [S1.1](#)
- **Acute post-traumatic headache attributed to moderate or severe head injury [S06]**
- **G44.880**
- **Diagnostic criteria:**
  - Headache, no typical characteristics known, fulfilling criteria C and D
  - Head trauma with at least one of the following:
    - Loss of consciousness for >30 minutes
    - Glasgow Coma Scale (GCS) <13
    - Post-traumatic amnesia for >48 hours
  - Imaging demonstration of a traumatic brain lesion (cerebral haematoma, intracerebral and/or subarachnoid haemorrhage, brain contusion and/or skull fracture)
  - Headache develops within 7 days after head trauma or after regaining consciousness following head trauma
  - One or other of the following:
    - Headache resolves within 3 months after head trauma
    - Headache persists but 3 months have not yet passed since head trauma

**Sample:**

**Acute Post-Traumatic Headache**

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  - One or other of the following:
    - Headache resolves within 3 months after head trauma
    - Headache persists but 3 months have not yet passed since head trauma
• Primary headache = Idiopathic, classic features

• Secondary headache = Defined by underlying cause

Treatment at 3 months
• Of those with headache at 3 months, 72% take medication and 93% find it partly or completely helpful
• 77% report taking abortive medication, 14% take preventive medication, 9% take both
• Only 10% of those with headache use other treatments
  – Including massage, biofeedback, acupuncture, exercise, stretching, PT, chiropractor, meditation

Frequency of Headache by Classification

Headache after TBI
• Detailed history (include pre-morbid, family)
  • C Character
  • O Onset
  • L Location
  • D Duration
  • E Exacerbate
  • R Relief
• Physical examination (head, neck, shoulders, vision, cranial nerves)
• Identify subtype of headache (migraine, migrainous, tension-type, cervicogenic, chronic daily, rebound, other)
General Treatment Approach

- Headache episodes = episodic treatment
  - Abortive therapy (short acting meds)
- 2+ headache days per week
  - At risk for medication rebound or overuse headache
  - Consider prophylactic therapy (daily meds)
  - Goal is decrease frequency and severity of HA
- Treat associated symptoms (nausea)

Migraine Meds

- Abortive / Acute
  - Acetaminophen, NSAIDs, Exedrin
  - Triptans (try different formulations)
- Prophylactic
  - AEDs:
    - Valproic acid
    - Topiramate
  - B-blockers:
    - Metoprolol, propranolol, timolol

Tension Meds

- Abortive / Acute
  - 1st NSAIDs, ASA, Acetaminophen
  - 2nd Excedrin (especially if severe)
- Prophylactic
  - 1st Amitriptyline
  - 2nd Mirtazapine or Venlafaxine
  - Other TCAs

Treatment

- Treat subtype of headache AND potential triggers
  - Migraine (abortive and prophylactic therapy)/stress, food, neck dysfunction, sleep disorder, medication overusage)
  - Tension type (physical therapy, analgesics, behavioral)
  - Cervicogenic (diagnostic and therapeutic blocks, therapy, NSAIDs)
- Always evaluate for potential pain mediators and treat (depression, insomnia)


Moderate to Severe TBI: Classic Complications, Treatment and Prognosis

Jennifer M. Zumsteg, MD
University of Washington
March 2015

Lecture Topics
Functional Prognosis after Severe TBI

Seizures       Cranial Neuropathies
Mass Lesions   Dizziness
Hydrocephalus  Endocrine Abnormalities
              Disorders of Sodium

= Consider learning more about these topics outside this lecture

Learning Objectives - 1
• Describe the threshold values for functional prognosis after severe TBI
• Define early and late post-traumatic seizures, general risk factors and guidelines for seizure prophylaxis
• Know the most common late intracranial mass lesion after TBI
• treatment

Learning Objectives - 2
• For posttraumatic hydrocephalus, list the common presenting signs and symptoms, typical time course, major risk factors and
• List cranial nerves frequently injured after blunt head trauma
• List major categories of post-traumatic dizziness and identify reasonable treatment strategies
Learning Objectives - 3

• Identify common causes and symptoms of sodium disorders after TBI
• List the relative frequency of other endocrine disorders after TBI

Prognosis after Severe TBI

• See lecture on severity and assessment tools

Q: Good recovery (based on GOS) after severe TBI is unlikely when:

1) Time to follow commands is greater than 2 weeks
2) Duration of post-traumatic amnesia is greater than 3 months
3) Age is greater than 45 years
4) MRI at one month indicates bilateral brain stem injury

Reminder: Functional Prognosis Mod-Severe TBI

• Threshold values → what’s unlikely to happen
  – Severe disability unlikely
    • Time to follow commands less than 2 weeks
    • Duration of PTA less than 2 months
  – Good recovery unlikely
    • Time to follow commands more than 4 weeks
    • Duration of PTA more than 3 months
    • 65+ years old
    • Bilateral brainstem lesions on MRI within 2 weeks
Reminder: TBI Outcome Studies → GOS

1 = DEAD

2 = VEGETATIVE STATE
   Unable to interact with environment; unresponsive

3 = SEVERE DISABILITY
   Able to follow commands/ unable to live independently

4 = MODERATE DISABILITY
   Able to live independently; unable to return to work or school

5 = GOOD RECOVERY
   Able to return to work or school

http://www.tbims.org/combi/gos/index.html

Reminder: Functional Prognosis after Severe TBI

GOS for some associated with worse outcomes:

1 = Diffuse lesions
Length of Coma

2 = Diffuse lesions associated with worse outcomes

3 = Severe disability initially when less than 2 weeks
   Diffuse recovery initially, then greater than 2 weeks
   Diffuse recovery, initially less than 2 weeks

4 = Severe disability when less than 2 months
   Diffuse recovery initially, then greater than 2 months

5 = Improved outcome when less than 2 years

A = Clear sign associated with worse outcomes
   Improved outcome


Treatment

• Neuro-recovery
  – Recent key studies

• (Rehabilitation interventions)

Quest for Neuro-recovery
Amantadine

- 184 subjects
  - minimally conscious or vegetative
- 4-16 weeks after TBI
- Amantadine or placebo for 4 weeks
  - Followed for another 2 weeks
- “Amantadine accelerated the pace of functional recovery during active treatment”

Citicoline

- TBI-Clinical Trials Network
- 1213 subjects within 24 hours of injury
- 90 days of citicoline or placebo
- No difference at 90 days
- No difference at 180 days
  …the quest continues
Rehabilitation Interventions

- Many opportunities
  - Community reintegration, return to work...
- Individualized care
  - PT → dizziness
  - OT → functional vision
  - SLP → Evidence-based cognitive rehabilitation
    - Cicerone KD, et al. Evidence-based cognitive rehabilitation
    - http://www.acrm.org/meetings/cognitive-rehab-training/

Classic Medical Complications

Seizures

Q: A 20-year-old man admitted with severe TBI secondary to penetrating head trauma should receive seizure prophylaxis with phenytoin for:

1) 3 days
2) 7 days
3) 7 months
4) Seizure prophylaxis is not indicated
Q: A patient has a seizure 3 days after a TBI. This is defined as a(n):

1) Immediate seizure
2) Early seizure
3) Late seizure
4) Posttraumatic epilepsy

Seizures

- Incidence: 2-2.4% entire population with TBI
  - Mild 1.5
  - Moderate 2.9
  - Severe 17.0

- Most initial seizures (80%) will occur in the first 2 years

Elevated Seizure Risk

- Mild – 5 years
- Moderate – 10 years
- Severe – 20+ years

  - *Risk elevated above the general population*

Posttraumatic Seizures

- Definitions:
  - (Immediate: at the time of injury)
  - Early: within 7 days after injury
  - Late: more than 7 days after injury

- Posttraumatic epilepsy = recurrent episodes
**Types of Seizures**

- Generalized tonic-clonic
- Partial or focal  
  - Most common type after TBI  
  - Simple - consciousness maintained  
  - Complex - consciousness impaired
- Anatomic correlates  
  - Temporal lobe (psychic, sensory, behavior)  
  - Orbitofrontal (automatisms, behavior)
- Non-epileptic seizures  
  - (pseudoseizures, psychogenic)

**Risk Factors for Seizures**

- Severity of trauma
- Penetrating head injuries
- Intracranial hematoma
- Depressed skull fracture
- Hemorrhagic contusion
- CNS operations
- Coma lasting more than 24 hours

**Seizure Management**

- Important to prevent further brain injury
- For moderate to severe TBI, prophylaxis with antiepileptic drugs (usually phenytoin) is for 7 days – longer duration does not help
- After 7 days, treat if seizure recurs  
  - Consider stopping AEDs if seizure free for 2 years
- Problems with AEDs: sedation, slowed learning, ataxia, behavior changes, allergies
Posttraumatic Seizures

- Differential diagnosis for seizures
- Acute seizure management
  - Many resolve without treatment
- Major characteristics, side effects, interactions, etc. of commonly used antiepileptic medications
Late Intracranial Mass Lesions

Q: The most common late-presenting mass lesion after TBI is:

1) Subdural hematoma
2) Hygroma
3) Intracerebral hemorrhage
4) Epidural hematoma
Late Intracranial Mass Lesions

- Subdural hematoma
  - Acute: up to 3 days
  - Subacute: 3-20 days
  - Chronic: 3 weeks or more

- Most common late mass lesion after TBI is SDH

Late Intracranial Mass Lesions

- Hygroma
- Epidural hematoma
- Intracerebral hemorrhage

*Imaging findings for intracranial mass lesions

Q: Select the descriptive pair that is NOT a correct match in subdural hematoma:

1) SDH 1 day after injury = acute
2) SDH 15 days after injury = subacute
3) SDH 22 days after injury = subacute
4) SDH 30 days after injury = chronic

Post-traumatic Hydrocephalus
Q: After TBI, ventriculomegaly on head CT is always diagnostic of hydrocephalus:

1) True
2) False

Q: What is the “classic” timing of post-traumatic hydrocephalus?

1) Within 7 days of injury
2) Within 30 days after injury
3) Within 3 months after injury
4) 1-5 years after injury

Post-traumatic Hydrocephalus

• Ventriculomegaly in more than 45% of persons with severe TBI
  – Ventriculomegaly (ex vacuo changes) vs. Hydrocephalus

• Usually Communicating Hydrocephalus:
  – Classic - dementia, ataxia, urinary incontinence
  – TBI - loss of upgaze, akinetic mutism
  – Headache, nausea, vomiting and lethargy or decreasing mental status

• Increased intracranial pressure
  – Cushing’s triad: HTN, bradycardia, hypoventilation

• Usually within 30 days

Post-traumatic Hydrocephalus

• Risk factors
  – Subarachnoid hemorrhage
  – More severe injuries
  – Skull fractures (depressed)
  – Infectious processes
Hydrocephalus

• Treatment:
  • Lumbar puncture
  • Shunt placement

Q: Which of the following is NOT one of Cushing’s triad?

1) Hypertension
2) Bradycardia
3) Hyperventilation
4) Hypoventilation

Cranial Neuropathies

Q: Which cranial nerve is NOT commonly injured from a TBI?

1) CN I
2) CN VII
3) CN VIII
4) CN X
Q: Which cranial nerve is most commonly injured after TBI?

1) CN I
2) CN III
3) CN IV
4) CN VI

Olfactory Nerve!

• CN I is not uncommonly injured after mild TBI
  — Safety
  — Work and hobby considerations

• Other cranial nerve findings should prompt consideration of more severe TBI or other associated pathology causing CN findings

Cranial Neuropathies

• Frequently injured in blunt head trauma
  — CN I: Olfactory nerve
  — CN VII: Facial nerve
  — CN VIII: Vestibulocochlear nerve

• Often injured in blunt head trauma
  — CN II: Optic nerve
  — CN III, IV, VI (relative frequency controversial)
    • Occulomotor, Trochlear, Abducens

Classic Palsies

• CN III
  — Exotropia, ptosis, mydriasis on affected side

• CN IV
  — Near vision and convergence difficult
  — Vertical diplopia, eye rotated outward at rest

• CN VI
  — Unable to abduct affected eye
    • Diplopia with lateral gaze to that side
Cranial Nerve Exam

• Additional resources provided at end of slide set

Dizziness

• 30-60%
  – Up to 100% with temporal bone fractures

Differential – Dizziness?

• Vertigo
• Balance impairment
• Vision changes
• Pre-syncpe/syncpe
• Associated with psychiatric diagnoses
• Other associations
  – Hyperventilation
  – Headache
Q: Dix Hallpike - A patient has the onset of nystagmus 15 seconds; nystagmus is suppressed with visual fixation. These are classic for:

1) Central vertigo
2) Peripheral vertigo
3) Psychogenic dizziness
4) Motor control disorder
Other Peripheral Dizziness

- Labyrinthine concussion
  - Hearing loss and continuous vertigo → general imbalance
  - Generally improves quickly
  - Rx: Time; Vestibular therapy

- Perilymphatic fistula
  - Disruption of middle and inner ear boundaries
  - Controversial
  - Hearing loss, vertigo and tinnitus
  - Symptoms may vary with pressure/valsalva
Dizziness

Treatment:
• Treat other issues: Visual correction, motor control, medication side effects
  – Vestibular therapy
  – Compensatory strategies
  – Otologist evaluation
  – Medication treatment
    • Antihistamines, phenothiazines, benzodiazepines
      – Concern for adverse effects on cognition in TBI

Q: Which of the following treatments for dizziness/blurriness should be used with caution in a person after TBI?

1) Vestibular therapy
2) Meclizine
3) Corrective lenses
4) Watch and wait

Syncope

Common causes of syncope:

Neurocardiovascular
• Migraine
• Vasovagal syncope
• Orthostatic hypotension
• Hyperventilation
• Postprandial
• Vasovagal syncope secondary to other causes
• Cardiac arrhythmias
• Syncope with disconnection
  – Cerebrovascular accident
  – Spinal cord trauma
  – Intracerebral hemorrhage
  – Subdural hematoma

Cardiovascular disease
• Hypertension
• Coronary artery disease
• Hypothyroidism
• Hyperglycemia
• Sickle cell disease
• Drug-induced hypotension

Drug- and alcohol-induced
• Central nervous system depressants
• Antihistamines
• Sedatives
• Antidepressants

Head injury
• Seizures
• Post-traumatic epilepsy

Neurologic disease
• Meningitis
• Neuromyelitis optica

Surgical
• Spinal surgery

Vestibular system
• Benign paroxysmal positional vertigo

Other
• Syncope of unclear origin

About 30% of patients presenting to the hospital
Q: Which disorder of sodium/water after TBI is consistent with serum hyponatremia and a urine sodium above 40 meq/L?

1) Diabetes insipidus
2) Cerebral salt wasting
3) Syndrome of inappropriate antidiuretic hormone (SIADH)
4) Nephrosis
Q: Which disorder of sodium after TBI is consistent with polyuria and mild hypernatremia?

1) Diabetes insipidus
2) Cerebral salt wasting
3) Syndrome of inappropriate antidiuretic hormone (SIADH)
4) Nephrosis

Disorders of Sodium

• ...and water

Task #1: Evaluate volume status

Is This Patient Hypovolemic?

http://depts.washington.edu/physdx/neck/physical.html
**Syndrome of Inappropriate Antidiuretic Hormone (SIADH)**

- Euvolemic hyponatremia, hypotonic
  - U osm > 100
    - Uosm > 300, NOT SIADH
  - Lethargy, nausea, seizures (or asymptomatic)

- Exclude: adrenal insufficiency, hypothyroidism, infection, drug causes
  - Clinical exclusion
  - Drugs: antipsychotics, antidepressants, ephedrine, vasopressin, dDAVP, MDMA

**SIADH**

- Too much free water for the amount of sodium

- Treat: free water restriction, free sodium use

**Q: Which descriptor does NOT fit for SIADH?**

1) Hypernatremia
2) Treat with water restriction
3) May be aggravated by carbamezepine
4) May present with seizure if severe

**Cerebral salt wasting**

- Hypovolemic hyponatremia, hypotonic
  - Renal losses
    - UNa > 20 mEq/L, FENa > 1%
  - Lethargy, nausea, seizures, (or asymptomatic)

- Exclude: salt wasting nephropathy, mineralocorticoid deficiency, extra-renal losses including GI, insensible and third-spacing (pancreatitis)
  - Drugs: thiazides
Q: What will likely occur if fluid restriction is used to treat hyponatremia secondary to cerebral salt wasting?

1) Sodium will correct
2) Sodium will remain stable
3) Patient will become more dehydrated
4) Patient will become volume overloaded

Cerebral salt wasting

- Results in renal losses of water and sodium. Unable to appropriately reabsorb.

   - Treatment:
     - Volume repletion
     - Salt tabs / other Na+ correction

   ** Fluid restriction will make the patient more dehydrated and may worsen the hyponatremia

Diabetes insipidus

- Euvolemic hypernatremia, hypertonic
  - Exclude hypovolemia
- Polydipsia, polyuria, fatigue, altered mental status
  - Symptomatic typically = impaired access to water
  - Often asymptomatic if mild

- Central diabetes insipidus
  - TBI 26% acute  6.9% chronic

Diabetes insipidus

- Central ADH deficiency
  - Hypothalamic or posterior pituitary injury; EtOH
  - Unable to reabsorb free water
  - Deficit of water relative to sodium

- Exclude: Nephrogenic causes including drugs (diuretics, lithium), hypercalcemia, severe hypokalemia, and GI losses

- Treatment: 1-d-amino-8-D-arginine-vasopressin (DDAVP) nasal spray, (carbamazepine)
  - Just replace missing hormone
SIADH Cerebral Salt Wasting Diabetes Insipidus

<table>
<thead>
<tr>
<th>Volume Status</th>
<th>* Euvolemic</th>
<th>* Hypovolemic</th>
<th>Euvolemic</th>
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<td>Serum Sodium</td>
<td>Hyponatremia</td>
<td>Hyponatremia</td>
<td>Hypernatremia</td>
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<tr>
<td>Helpful Labs</td>
<td>U osm &gt; 100, but &lt; 300</td>
<td>Unna &gt; 20 mEq/L, FENa &gt; 1%</td>
<td>Uosm &lt;800, Uosm&lt; 300 = complete DI</td>
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<tr>
<td>Underlying Driver</td>
<td>Excess ADH: Reabsorbing too much free water</td>
<td>Renal water and sodium losses: Unable to apop. concentrate</td>
<td>Lack of ADH, lack of access to free water to make up it</td>
</tr>
<tr>
<td>Ddx includes</td>
<td>Glucocorticoid insuf., hypothyroid, infection, drugs</td>
<td>Mineralocorticoid insuf., drugs, extrarenal losses</td>
<td>Renal and GI losses, EOH, protein malnutrition</td>
</tr>
<tr>
<td>Treatment</td>
<td>Free water restrict -Increase sodium intake (IV saline)</td>
<td>Regulate water volume and sodium</td>
<td>Free water access DDAVP</td>
</tr>
</tbody>
</table>

**Major causes of hyponatremia**

Unplaced water loss (which requires an impairment in either thirst or access to water)
- Insensible and sweat losses
- Gastrointestinal losses
- Central or nephrogenic diabetes insipidus
- Osmotic diuresis
- Glucose in uncontrolled diabetes mellitus
- Losses in high-protein tube feedings
- Wound
- Hypothalamic lesions impairing thirst or osmoreceptor function
- Primary hypothyroidism
- Nephrotic syndrome or inappropriate antidiuretic hormone (ADH) secretion

Water loss into cells
- Severe exercise or seizures
- Sodium overload
- Intake or administration of hypertonic sodium solutions

**Endocrine Abnormalities after TBI**

- Hypothyroidism
- Hypopituitarism
- Hypoadrenalism
Hypothalamus Functions

- Autonomic nervous system
- Limbic system; regulate emotional and behavioral patterns
- Regulates eating and drinking
- Controls body temperature and regulates diurnal rhythms
- Controls pituitary gland secretions

Q: Most common deficiency after TBI is:

1) LH/FSH
2) Growth Hormone
3) ACTH
4) TSH
Q: Least common deficiency after TBI is:

1) LH/FSH
2) Growth Hormone
3) ACTH
4) TSH

Endocrine Abnormalities

- Approximately 20% of persons with moderate to severe injuries
  - LH/FSH and GH deficiencies > ACTH > TSH
- Hypothalamic → pituitary signaling
- Anterior vs. posterior pituitary

Q: Which of the following is NOT a clear risk factor for endocrine dysfunction after TBI?

1) Increased severity of injury
2) Diffuse axonal injury
3) Prolonged ICU stay
4) Nasal bone fractures

Endocrine Risk Factors

- Severity of TBI, basal skull fractures, diffuse axonal injury, increased intracranial pressure, prolonged stay in ICU
- TBI (pooled prevalence)
  - Severe 35.3%
  - Moderate 10.9%
  - Mild 16.8%
Endocrine

• Trend toward improvement in pituitary function over time

• In minority, worsen over time

• New deficiencies rare after 6 months from injury

Screening after TBI

• Controversial
  – Variability in studies
    • Different cut-offs used...

Screening and Treatment

• Growth Hormone deficiency
  – No early treatment
  – Confirm deficiency after other deficiencies are treated

• Isolated hypogonadism not a clinical emergency
  – Confirm before replacement started

Screening / Workup and Treatment

• Rehab (subacute/chronic)
  – 3 month for persons with risk factors
    • If abnormal but borderline, repeat after one month
  – Persistent fatigue, dizziness, sleep disturbance, weight gain: TSH, FT3, FT4, AM cortisol, IGF-1
  – Treat hypothyroidism, referral to endocrine if any abnormal or if IGF-1 is more than 2SD below the laboratory norm for their age group
Endocrine - Amenorrhea

- For “prolonged” amenorrhea: (~ 6 months)
  - LH, FSH Refer if abnormal

- Should be re-evaluated at 1 year to determine necessity of continued treatment

- Testosterone deficiency

Breathe...

Other Complications

- Airway and pulmonary management
- Autonomic storming
- Bowel and bladder dysfunction
- Coma assessment and management
- CNS infections after TBI
- Dysphagia / nutrition
- Headaches
- Heterotopic ossification
- Hypertension

- Mood disturbances
- Other pain syndromes
- Other behavioral and psychiatric conditions (including PTSD and agitation)
- Sleep
- Spasticity /contracture
- Traumatic aneurysm
- Venous thromboembolic disease and DVT prophylaxis
Other related topics

- Biomarkers
- Pediatric considerations
- Geriatric considerations

Discussion

References

Supplemental Resources...

Article: How to remember brainstem anatomy...

Actions of extraocular muscles

<table>
<thead>
<tr>
<th>Nerve and muscle</th>
<th>Primary action</th>
<th>Secondary action</th>
<th>Tertiary action</th>
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</thead>
<tbody>
<tr>
<td>CN III Superior rectus</td>
<td>Elevation (maximal on lateral gaze)</td>
<td>Intorsion</td>
<td>Adduction</td>
</tr>
<tr>
<td>CN III Inferior rectus</td>
<td>Depression (maximal on lateral gaze)</td>
<td>Extorsion</td>
<td>Adduction</td>
</tr>
<tr>
<td>CN IV Medial rectus</td>
<td>Adduction</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CN IV Inferior oblique</td>
<td>Eversion</td>
<td>Abduction</td>
<td></td>
</tr>
<tr>
<td>CN IV Superior oblique</td>
<td>Inversion</td>
<td>Depression (maximal on medial gaze)</td>
<td></td>
</tr>
<tr>
<td>CN VI Lateral rectus</td>
<td>Abduction</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Nonpupil-sparing third nerve palsy

Right mydriasis in a patient with a right third nerve palsy secondary to a posterior communicating aneurysm. The patient also had a mild ptosis and complained of diplopia with reduced adduction, elevation, and depression of the right eye. Abduction and intorsion were normal in the right eye.

Partial third nerve palsy

This patient has ptosis of the right upper eyelid. Note that the right eye does not elevate well, indicating a superior division third nerve palsy.

Third nerve anatomy

The third cranial nerve begins as a nucleus in the midbrain. The fascicle of the third nerve leaves the midbrain and passes ventrally through the cavernous sinus before exiting the skull through the oculomotor foramen in the sphenoid bone. It then enters the intracranial space, passes into the lateral wall of the cavernous sinus, and finally divides into its three terminal branches: motor (oculomotor nerve), parasympathetic (pterygopalatine ganglion), and sympathetic (communicating trigeminal). The parasympathetic fibers pass to the pterygopalatine ganglion and the sympathetic fibers pass through the carotid canal to innervate the ciliary ganglion, which innervates the iris and ciliary body in the eye. The function of the third nerve is to innervate the muscles of the extraocular muscles, orbit, and the dilator pupillae muscle.

This patient has ptosis of the right upper eyelid. Note that the right eye does not elevate well, indicating a superior division third nerve palsy.

This patient has ptosis of the right upper eyelid. Note that the right eye does not elevate well, indicating a superior division third nerve palsy.
### Causes of binocular vertical diplopia and hypertropia hypotropia

**Superior oblique tendonitis**
- Superior oblique tenosynovitis (retro-orbital pain)
- Tenon's cyst
- Vertical or oblique oculomotor nerve palsy

**Stapedius muscle**
- Stapedius muscle atrophy
- Stapedius muscle palsy

**Nystagmus**
- Pendular nystagmus
- Fixation-nystagmus nystagmus

**Cerebral cortex**
- Cerebral cortex lesion

**Meningeal processes causing vertical eye misalignment**
- Dura mater
- Chronic sinusitis
- Meningocele

### Causes of acquired binocular horizontal diplopia

#### Causes of esotropia
- Childhood strabismus syndrome (see Table 2)
- Change of angle of presenting diaphanoscopy
- Suppression of a long-standing esotropia
- Consecutive esotropia (after strabismus surgery)
- Optic atrophy or central retinal artery occlusion
- Sensory esotropia (usually not associated with diplopia)
- Dystrophies of muscles and connective tissue
- Ciliary muscle (internal pseudotumor)
- Thyroid eye disease
- Myasthenia gravis
- Mechanical internal wall weakness
- Isolated weakness of lateral rectus muscle
- Myokymia
- Progressive external ophthalmoplegia syndrome
- Other orbital disease processes

#### Causes of exotropia
- Childhood strabismus syndrome (see Table 2)
- Change of angle of presenting diaphanoscopy
- Loss of suppression
- Suppression of a long-standing exotropia
- Consecutive exotropia (after strabismus surgery)
- Optic atrophy or central retinal artery occlusion
- Sensory exotropia (usually not associated with diplopia)
- Disorders of the muscles
- Orbital muscle (abducens paralysis)
- Thyroid eye disease (Graves' disease)
- Thyroid eye disease (scleroderma)
- Horner's syndrome
- Mechanical internal wall weakness
- Isolated weakness of lateral rectus muscle
- Muscle tumors
- Progressive external ophthalmoplegia
- Other orbital disease processes
- Disorders of cranial nerves

#### Other causes
- Optic nerve palsy
- Optic nerve hypoplasia
- Central disorders
- Optic nerve hypoplasia
- Demyelinating disorders
- Optic atrophy or central retinal artery occlusion
- Thyroid eye disease (Graves' disease)
- Thyroid eye disease (scleroderma)
- Horner's syndrome
- Mechanical internal wall weakness
- Isolated weakness of lateral rectus muscle
- Muscle tumors
- Progressive external ophthalmoplegia
- Other orbital disease processes
- Disorders of cranial nerves

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Neuropharmacology of Traumatic Brain Injury

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Neuropsychiatric Sequelae

- Delirium
- Depression / Apathy
- Mania
- Anxiety
- Psychosis
- Cognitive Impairment
- Aggression, Agitation, Impulsivity

Neurobiological Mechanisms

- Frontal and temporal lobe lesions lead to neuropsychiatric syndromes

- Diffuse axonal injury, hypoxia, hypometabolism, free radical and excitotoxic neurotransmitter release
  - Can affect serotonin, norepinephrine, dopamine, acetylcholine, and GABA systems

Examples of Neuropsychiatric Syndromes Associated with Neuroanatomical Lesions

- Lateral orbital pre-frontal cortex
  - Irritability
  - Mood lability
  - Mania

- Anterior cingulate pre-frontal cortex
  - Apathy
  - Akinetic mutism

- Dorsolateral pre-frontal cortex
  - Poor memory search
  - Poor set-shifting / maintenance

- Temporal Lobe
  - Memory impairment
  - Psychosis
  - Mood lability
  - Aggression

- Hypothalamus
  - Sexual behavior
  - Aggression
Neuropsychiatric Evaluation and Treatment: Etiologies

**Psychiatric**
- Premorbid
- Psych disorders & sxas.
- Personality traits
- Coping styles
- Substance Abuse
- Medication side effects
- Interactions
- Psychodynamic signif. of neurologic illness
- Family psych. history

**Neurologic/Medical**
- Neurologic illness
- Lesion location, size, pathophysiology
- Other medical illness
- Other indirect sequelae (e.g., pain, sleep disturb)
- Medication side effects
- Interactions
- Psychodynamic signif. of neuropsychiatric sxas., disability and treatments

**Social**
- Social, family, vocation
- Rehabilitation situation and stressors
- Functional impairment
- Medicolegal
- Medication side effects & interactions
- Psychodynamic signif. & interactions of neurologic illness

Roy-Byrne P, Fann JR. APA Textbook of Neuropsychiatry, 1997

Neuropsychiatric Evaluation and Treatment: Workup

**Psychiatric**
- Psychiatric history & examination
- Neuropsychological testing
- Psychodynamic signif. of neurologic illness
- Substance Abuse
- Other indirect sequelae
- Family psych. history

**Neurologic/Medical**
- Medical history and physical examination
- Appropriate lab tests
- e.g., CBC, med blood levels, CT/MRI, EEG
- Medicolegal
- Medication allergies
- Physical signs & sxas.
- Physiologic response (e.g., vital signs)
- Appropriate lab tests (e.g., CBC, medication blood levels, EEG)
- Rehabilitation
- Maximize support system

**Social**
- Interview family, friends, caregivers
- Assess level of care & supervision available
- Assess rehab needs & progress

Neuropsychiatric Evaluation and Treatment: Follow-up

**Psychiatric**
- Frequent pharmacologic monitoring
- Psychotherapy
- Intermittent cognitive assessments
- Support Groups
- Use validated assessment tools

**Neurologic/Medical**
- Physical signs & sxas.
- Physiologic response (e.g., vital signs)
- Appropriate lab tests (e.g., CBC, medication blood levels, EEG)

**Social**
- Rehabilitation
- Maximize support system

Neuropsychiatric History

- Characterize diagnosis/ symptoms as precisely as possible
- Psychiatric symptoms may not fit DSM-5 criteria
- Focus on functional impairment
- Document and rate symptoms (use validated instruments, if available)
- Assess pre-TBI personality, coping, psychiatric history (anxiolytic use is RF for TBI (Fann et al, 2002)
- Talk with family, friends, caregivers
- How has life changed since TBI?
  - Impact on self-image, cognition, function
- Thorough review of medical and psychiatric symptoms
- Assess level of care and support available
Neuropsychiatric Treatment

- Use Biopsychosocial Approach
- Define realistic treatment endpoints
- What’s worked in the past?
- Treat maximum signs and symptoms with fewest possible medications
- TBI patients more sensitive to side effects
  START LOW, GO SLOW, BUT GO
- May still need maximum doses
- Therapeutic onset may be latent
- Involve support system

Psychiatric Illness in Adult HMO Enrollees (N=939 with TBI, 2817 controls)

Fann et al. Arch Gen Psychiatry 2004; 61:53-61

Common Comorbidities in TBI

- Anxiety / Worry / Panic
- Depression
- Insomnia
- Pain
- Irritability / Anger
- Fatigue

Polypharmacy
**Common Polypharmacy Pitfalls**

- Anxiety / Worry / Panic
  - Benzodiazepines
- Depression
  - Antidepressants
- Insomnia
  - Sedative-hypnotics
- Pain
  - Opioids, gabapentin
- Irritability / Anger
  - Beta-blockers, antipsychotics
- Fatigue
  - Psychostimulant

**Potential Consequences of Polypharmacy**

- Drug-drug interactions
- Accidental or volitional overdose
- Non-adherence
- Cumulative adverse effects
  - E.g., sedation, lightheadedness, cognitive impairment, fatigue
- Delirium
- Accidents (falls, MVAs)
- Unnecessary health care utilization & costs

**Management Opportunities**

<table>
<thead>
<tr>
<th></th>
<th>Anxiety</th>
<th>Depress</th>
<th>Insomnia</th>
<th>Pain</th>
<th>Irritable / Anger</th>
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</tr>
</tbody>
</table>

**Delirium**

- Increased risk in patients with TBI
- Undiagnosed in 32-67% of patients
  - Often missed in both inpatient and outpatient settings
  - Associated with 10-65% mortality
  - Up to 25% of delirious medical patients die during hospitalization and 37% within 1-3 months of onset
  - Can lead to self-injurious behavior, decreased self-management, caregiver management problems
  - Associated with increased length of hospital stay and increased risk of institutional placement
  - Other terms used to denote delirium: acute confusional state, intensive care unit (ICU) psychosis, metabolic encephalopathy organic brain syndrome, sundowning, toxic encephalopathy
Delirium

- Identify and correct underlying cause
  - TBI increases a person’s vulnerability
    - e.g., seizures, hydrocephalus, hygromas, hemorrhage, drug side effect or interactions, endocrine (hypothalamic, pituitary dysfunction), metabolic (e.g., sodium, glucose), infections
- Pharmacologic management
  - Antipsychotics
    » Haloperidol (e.g., IV), droperidol, risperidone, olanzapine, quetiapine (taper 7 – 10 days after return to baseline)
    » May cause QTc prolongation, metabolic syndrome, sudden cardiac death in elderly
  - Benzodiazepines (combined with antipsychotics), alcohol or sedative withdrawal
    » Lorazepam
- Minimize polypharmacy
- Medical management
  - Frequent monitoring of safety, vital signs, mental status and physical exams
  - Maintain proper nutritional, electrolyte, and fluid balance

Depression / Apathy

- Prevalence of major depression 44.3% *
  - Assess pre-injury depression and alcohol use
  - Use ‘inclusive’ diagnostic technique
  - May occur acutely or post-acute
  - Not directly related to TBI severity
- Apathy alone - prevalence 10%
  - disinterest, disengagement, inertia, lack of motivation, lack of emotional responsivity

MDD & PTSD after TBI

- Army soldiers: (Hoge et al, 2008)
  - Mild TBI with LOC: 43.9% PTSD, 22.9% MDD
  - Mild TBI without LOC: 27.3% PTSD, 8.4% MDD
  - Other injuries: 16.2% PTSD, 6.6% MDD
- Civilians:
  - MDD Point prevalence 26-31%
  - MDD Period prevalence 42-53% within the first year, 61% within the first 7 years after TBI.
  - Rates of depression are not associated with TBI severity
  - Rates of PTSD following mild TBI (11-24%) are about twice as high as rates following moderate to severe TBI,

Impact of Depression on Outcomes

Depression after TBI associated with:

- Poorer cognitive functioning (Rappoport et al., 2005)
- Lower health status and greater functional disability (Christensen et al., 1994; Levin et al 2001; Fann et al., 1995; Hibbard et al., 2004; Rappoport et al., 2003)
- More post-concussive symptoms (Fann et al., 1995; Rappoport et al., 2005)
- Increased aggressive behavior and anxiety (Tateno et al., 2003; Jorge et al., 2004; Fann et al., 1995)
- Poorer recovery and return to work (Mooney et al., 2005; Hoge et al, 2008)
- Higher rates of suicidal plans (Kihl et al., 2001), 8 times more suicide attempts (Silver et al., 2001), 3-4 times more completed suicides (Tsakalou and Engberg, 2001) than in non-brain injured controls
Importance of Depression & PTSD

- Hoge et al, NEJM 2008
  - Many putative mild TBI-related symptoms may overlap with and be mediated, at least in part, by depression and PTSD
    - Overall Health
    - Missed Workdays due to illness
    - Medical Visits due to physical condition
    - Somatic & post-concussive symptoms (including memory & concentration problems)

Pharmacotherapy Trials in TBI

- Systematic Review: 13 studies
- One class I study (Ashman et al., 2009), N=52
  - showed trends toward superiority of sertraline over placebo
  - temporally far removed from TBI (18 yrs)
  - underpowered to examine predictors of response
- Cannot assume standard treatments have same efficacy and tolerability in TBI
- SSRIs were the best tolerated
- 6 studies of electroconvulsive tx, acupuncture, magnetic field exposure, biofeedback

Depression / Apathy

- Selective serotonin re-uptake inhibitors (SSRIs)
  - sertraline
  - paroxetine
  - fluoxetine
  - citalopram
  - escitalopram
  - venlafaxine, duloxetine, levomilnacipran (help with pain)
  - bupropion (may decrease seizure threshold)
  - nefazodone (may be too sedating, liver toxicity)
  - mirtazapine (may be too sedating)
  - Tricyclics: nortriptyline, desipramine (blood levels)
  - methylphenidate, dextroamphetamine
  - Electroconvulsive Therapy – consider less frequent, nondominant unilateral

- Apathy: Dopaminergic agents - methylpyphenidate, pemoline, bupropion, amantadine, bromocriptine, selegiline, modafinil (no RCTs in TBI)

Pilot study of sertraline after Mild TBI (N=15)
(Hamilton Depression Scale)

Mania

- Prevalence of Bipolar Disorder 4.2% *
- High rate of irritability, “emotional incontinence”
  - Distinguish from “Pseudobulbar Affect”
- May be associated with epileptiform activity
- Potential interaction of genetic loading, right hemisphere lesions, and anterior subcortical atrophy


Mania

- Acute
  - Benzodiazepines
  - Antipsychotics
    - olanzapine, risperidone, quetiapine, clozapine
  - Anticonvulsants
    - valproate
  - Electroconvulsive Therapy
- Chronic
  - valproate
  - carbamazepine
  - lamotrigine
  - lithium carbonate (neurotoxicity)
  - gabapentin, topiramate (adjunctive treatments)

Pseudobulbar Affect

A neurologic condition characterized by episodes of crying or laughing that are sudden, frequent, and involuntary

Occurs in patients with TBI, MS, ALS, stroke, and certain other neurologic conditions

FDA-approved in 2011 – Nuedexta ®
  - Dextromethorphan (20mg) – modulates glutamate
    +
  - Quinidine (10mg) – metabolic inhibitor
Anxiety & Related Disorders after TBI

- Often comorbid with and prolongs course of depression, substance use
- Panic Disorder: Prevalence 9.2%
- Generalized Anxiety Disorder: Prevalence 9.1%
- Obsessive-Compulsive Disorder: Prevalence 6.4%
- Posttraumatic Stress Disorder: Prevalence 14.1%
  - Intrusions, Avoidance, Cognitions/Mood, Arousal
  - > 1 month, causes significant distress or impairment
  - More prevalent in mild TBI


Anxiety

Medications
- Benzodiazepines: use lower doses (~50% typical dose), taper when possible
  - e.g., clonazepam, lorazepam, alprazolam
  - Watch for cognitive impairment, disinhibition, dependence
- Buspirone (for Generalized Anxiety Disorder)
- Antidepressants: SSRIs, SNRIs, mirtazapine, TCAs, trazodone, nefazodone, MAOIs
- Beta-blockers, verapamil, clonidine
- Prazosin (for PTSD nightmares)
- Anticonvulsants: valproate, gabapentin, pregabalin, vigabatrin, tiagabine have some anxiolytic effects
- Antihistamines: hydroxyzine, diphenhydramine
- Antipsychotic augmentation: olanzapine, quetiapine, risperidone

Psychosocial: CBT, Behavioral Activation, couples/family, group

Psychosis

- Hallucinations, delusions, thought disorder
- Immediate or latent onset
- Symptoms may resemble schizophrenia: prevalence 0.7%
- Schizophrenics have increased risk of TBI pre-dating psychosis
- Patients developing schizophrenic-like psychosis over 15-20 years is 0.7-9.8%


Psychosis

- Antipsychotics
  - First generation: e.g. haloperidol, chlorpromazine (seizures)
  - Second generation: e.g., risperidone
  - Third generation: e.g., olanzapine (2 case reports), quetiapine, ziprasidone, aripiprazole, paliperidone, clozapine (seizures)
- Start with low doses (e.g., Risperidone 0.5mg qHS)
- TBI pts have high risk of anticholinergic and extrapyramidal side effects
- May cause QTc prolongation, increased sudden death in elderly, metabolic syndrome
- Use sparingly - may impede neuronal recovery acutely (from animal data)
Cognitive Impairment

- Common problems
  - Concentration and attention
  - Memory
  - Speed of information processing
  - Mental flexibility
  - Executive functioning
  - Neurolinguistic

- Association with Alzheimer’s Disease suggested
- May be associated with other psychiatric syndromes (e.g., depression, anxiety, psychosis, insomnia) – treating these may improve cognition

Cognitive Impairment

May improve recovery

- Stimulants
  - methylphenidate, dextroamphetamine, caffeine
- Nonstimulant dopamine enhancers
  - amantadine, bromocriptine, pramipexole, L-dopa/carbidopa
- Acetylcholinesterase inhibitors
  - physostigmine, donepezil, rivastigmine, galantamine
- Antidepressants
  - sertraline, fluoxetine, milnacipran (SNRI)
- Others
  - Citicoline (recent negative study JAMA 2012), gangliosides, pergolide, selegiline, apomorphine, phenylpropanolamine, naltrexone, atomoxetine, vasopressin, modafinil, antioxidants

Writer & Schillerstrom, J Neuropsychiatry Clin Neurosci 2009

Cognitive Impairment

May impede recovery

haloperidol
phenothiazines
prazosin
clonidine
phenoxybenzamine
GABAergic agents
benzodiazepines
Phenytoin
Carbamazepine?
Topiramate?
phenobarbital
Idazoxan

Cognitive Impairment

Aggression, Irritability, Impulsivity

- Up to 70% within 1 year of TBI
- May last over 10-15 years
- Interview family and caregivers
- Characteristic features
  - Reactive - Explosive
  - Non-reflective - Periodic
  - Non-purposeful - Ego-dystonic
- Treat other underlying etiologies (e.g., bipolar, PTSD)
- Also use behavioral interventions
Aggression, Agitation, Impulsivity  
(none FDA approved for this indication)
- Acute  
  Antipsychotics (e.g., quetiapine 25-100mg bid)  
  Benzodiazepines (e.g., clonazepam 0.5mg bid)  
- Chronic  
  Beta-blockers - e.g. propranolol – may need up to 200mg/d in some cases, pindolol, nadolol  
  valproate, carbamazepine, gabapentin, lamotrigine  
  Lithium (neurotoxicity, narrow therapeutic window)  
  buspirone  
  Serotonergic antidepressants (e.g., SSRIs, trazodone)  
  tricyclic antidepressants (e.g., nortriptyline, desipramine)  
  Antipsychotics (esp. second and third generation)  
  amantadine, bromocriptine, bupropion  
  clonidine, methylphenidate, naltrexone, estrogen, dronabinol

Pilot study of sertraline (N=15)  
Brief Anger / Aggression Questionnaire (BAAQ)

Hypopituitarism
- Unrelated to TBI severity in most studies  
- Growth hormone deficiency, hypogonadism  
- Can be assoc. with anxiety, depression, fatigue, irritability, insomnia, sexual dysfunction, cognitive impairment  
- Assess GH-IGF-1 axis  
- Hormone replacement may help

Conclusions
- Neuropsychiatric syndromes are common after TBI  
- They can present in many different ways  
- They can significantly increase distress, disability, and health care utilization  
- Use biopsychosocial and multidisciplinary approach  
- Treat as many symptoms with as few medications as possible  
- Monitor systematically and longitudinally
References


