Traumatic Brain Injury

Epidemiology and Pathophysiology

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Disclosures

None
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 and Secondary
    • Focal and Diffuse
Pre-test

TECHNICAL DIFFICULTIES

REPAIRS UNDERWAY
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. Gray matter
  C. Basal ganglia
  D. Internal capsule
Clinical Diagnosis of TBI
TBI: Definition

- Injury to the head
  - Reasonable mechanism
  - Subjective/objective report
  - Imaging findings

- Loss / Decreased level of consciousness
  - Subjective report
  - Objective report

- Objective Neuro/psych findings
  - Data collection

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

- Injury to the head
  - Reasonable mechanism
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  - Imaging findings

- Loss / Decreased level of consciousness
  - Subjective report
  - Objective report
  - Data collection

- Objective Neuro/psych findings
  - Observed?
  - Intoxicated?
  - Hypotensive?
  - Baseline Symptoms?

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
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
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 causes 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, 3\textsuperscript{rd} 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
Epidemiology: Deaths

- **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
- **Leading cause of death overall:**
  - Firearm
Epidemiology: non-fatal TBI (ED)

Percent Distributions of TBI-related Emergency Department Visits by Age Group and Injury Mechanism — United States, 2006–2010

- 0–4 years: Falls (80%), Motor Vehicle Traffic (10%), Struck by/Against (5%), Assault (5%), All Other Causes (5%), Unknown (5%)
- 5–14 years: Falls (70%), Motor Vehicle Traffic (20%), Struck by/Against (10%), Assault (10%), All Other Causes (10%), Unknown (10%)
- 15–24 years: Falls (60%), Motor Vehicle Traffic (30%), Struck by/Against (10%), Assault (5%), All Other Causes (5%), Unknown (5%)
- 25–44 years: Falls (50%), Motor Vehicle Traffic (30%), Struck by/Against (20%), Assault (10%), All Other Causes (5%), Unknown (5%)
- 45–64 years: Falls (40%), Motor Vehicle Traffic (40%), Struck by/Against (20%), Assault (10%), All Other Causes (5%), Unknown (5%)
- ≥ 65 years: Falls (30%), Motor Vehicle Traffic (30%), Struck by/Against (20%), Assault (20%), All Other Causes (10%), Unknown (10%)
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)
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

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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
Primary Injury
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
CT scan of the brain depicting cerebral contusions. The basal frontal areas (as shown) are particularly susceptible.

Reproduced with permission from: J Claude Hemphill III, MD and Nicholas Phan, MD, FRCSC.
Primary Injury

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

Case courtesy of Dr Alexandra Stanislavsky, Radiopaedia.org
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
  – Principal mechanical force responsible: **rotational acceleration** of the brain

Diffuse axonal injury

CT scan of the brain showing diffuse axonal injury (DAI). Note the deep shearing-type injury in or near the white matter of the left internal capsule (arrow).

Reproduced with permission from: J Claude Hemphill II, MD and Nicholas Phan, MD, FRCSC. Case courtesy of Dr Alexandra Stanislavsky, Radiopaedia.org
Diffuse axonal injury.
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: 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

Primary Injury: DAI

• Acute post-traumatic stage: appear as swollen fibers containing accumulated cytoskeletal proteins

• Over time, swollen axons eventually undergo complete axotomy and undergo Wallerian degeneration
  – associated with death of oligodendrocytes

Fig. 1. Representative images of axonal pathology following TBI in humans identified using amyloid precursor protein (APP) immunohistochemistry. (a) Extensive axonal pathology with classic varicosities and axonal bulb formation in the corpus callosum of a young male who died 10 h following blunt force trauma to the head.

Primary Injury

• **Impact depolarization**
  – Physical force leading to glutamate release (excitatory)
    • leads to **excitotoxicity (secondary injury)**
    • Even in mild TBI
Focal Injury
Pathological Injury Classification

• Anatomical:
  – Focal
  – Diffuse

• Pathophysiological:
  – Primary
  – Secondary

• Mechanistic:
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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
CT scan demonstrating a right epidural hematoma (EDH, arrow). Note the lenticular shape.

Reproduced with permission from: J Claude Hemphill III, MD and Nicholas Phan, MD, FRCSC.
CT scan showing a left acute subdural hematoma (SDH, arrow). Subdural hematomas are typically crescent-shaped. In this case the SDH is causing significant mass effect and shift of midline structures to the right.

Reproduced with permission from: J Claude Hemphill III, MD and Nicholas Phan, MD, FRCSC.
CT scan demonstrates the typical findings of a nonaneurysmal perimesencephalic subarachnoid hemorrhage. Note the predominance of hemorrhage in the interpeduncular fossa (arrow).

*Courtesy of Guy Rordorf, MD.*
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

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

Impact (primary)

Surge of K+ and glutamate (primary)

Brain Swelling

Increased ICP and Decreased CPP

Cellular injury and death
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

Cell Death

- Apoptotic and necrotic neurons seen within contusions in the acute post-traumatic period and in regions remote from the site of impact in the days and weeks after trauma
- Degenerating oligodendrocytes and astrocytes also seen within injured white matter tracks

DAI grade

• 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
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 maybe **early** post-injury cholinergic **excess** followed by development of **late** cerebral cholinergic **deficits**
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%
- Struck by/against, 15.5%
- Unknown/Other, 19.0%
- Motor vehicle traffic, 14.3%
- Assaults, 10.7%
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
Question 3

• Diffuse axonal injury is classically seen in following structures except:
  A. Corpus callosum
  B. Gray matter
  C. Basal ganglia
  D. Internal capsule
Primary Injury

• Diffuse Axonal Injury
  – Classically affects **white matter** in areas including corpus callosum, basal ganglia, thalamus, cerebral hemispheres, internal capsule, and brainstem

Question 4

• Grade 2 Diffuse axonal injury imaging indicates a focal lesion in the:

A. Corpus callosum
B. Brainstem lesion
C. No Focal injury on imaging
D. All of the above
E. None of the above
DAI grade

• 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
Question 5

• Which of the following is an example of a primary mechanism of brain injury?
  A. Cerebral edema
  B. Focal ischemic injury
  C. Free radical damage
  D. Diffuse axonal injury
Primary Mechanism

• Traumatic axonal injury, also refer to as diffuse axonal injury, is a source of primary traumatic brain injury.
• DAI occurs with shearing forces of white matter
• Other sources of primary brain injury mechanism include cerebral contusions of gray matter, vascular injuries, contusions, and laceration that occurred at the moment of impact
Question 6

• In diffuse axonal injury, influx of which ion is responsible for inducing cytoskeletal degradation?
  A. Na$^+$
  B. K$^+$
  C. Ca$^{2+}$
  D. H$^+$
Diffuse axonal injury

- Influx of Ca^{2+} causes activation of the calpain (calcium-activated neutral proteases) system which results in proteolysis of intracellular proteins including cytoskeletal proteins.
- In in vitro study, activation of calpain may be predominantly associated with necrotic cell death.
- In vitro study also suggest that low intracellular Ca^{2+} may selectively initiate apoptotic pathways.
- It maybe more complicated in traumatic insults.

Thank you!
Reference


