Post Traumatic Epilepsy in Children

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Disclosure

• I have no financial relationship with any manufacturer of any commercial product and/or provider of commercial services discussed in this CME activity.

• I intend to discuss antiepileptic medication use in children, some of which is not FDA approved.
Background

• Traumatic brain injury (TBI) is the most common cause of morbidity and mortality in children and young adults.
• 90% of injury related deaths are due to TBI
• 1.4 million TBIs occur annually in the U.S.
  • 1 million treated in the ED
  • 300,000 hospitalized and survive
  • 50 – 75,000 die
• Ages most at risk are the very young and the very old
• Direct and indirect costs are $57.8 billion annually in the US.
  • Average inpatient cost over $150,000
Background

- Of 14 states surveyed, by the CDC, Arizona had the second highest rate of TBI:
  - Average: 70 per 100,000
  - AZ: 85 per 100,000
- Consequences of TBI:
  - Death
  - Physical disability
  - Epilepsy (20% of symptomatic type)
  - Behavioral Disorders
  - Migraine
  - Memory impairment
  - Alzheimer’s Disease
  - Impaired concentration and learning
  - Sleep disorders
  - Endocrine abnormalities
Epidemiology

• Males are twice as likely as females to sustain a head injury.

• Football is the most common cause of sports-related injury.

• ATV accidents result in a disproportionate number of childhood head injury and death.

• Children less than 2 years old are at highest risk for non-accidental trauma.
Types of Head Injury

- Scalp hematoma/ laceration
- Skull fracture
- Intracranial hemorrhage
  - Subarachnoid hemorrhage
  - Subdural hematoma
  - Epidural hematoma
- Cerebral contusion
- Diffuse axonal injury
- Penetrating injury
Skull Fracture
Intracranial Hemorrhage
Penetrating Injury
Diffuse Axonal Injury
Diffuse Axonal Injury

- Occurs as a result of acceleration/deceleration or rotational forces
  - Shearing forces affect the white matter tracts
- Greater than 50% of severe TBI cases have evidence of DAI
  - Common cause of unconsciousness/coma
  - 90% with severe DAI never regain consciousness
- Not easily detected on imaging studies
Pathophysicsology of TBI

• Primary Injury (initial mechanical force)
  • Acceleration/ deceleration injury
  • Linear forces
  • Rotational forces
    • All result in physical disruption of cell membranes.
    • All head injury has some degree of axonal damage.

• Secondary Injury
  • Hypoxia, ischemia, reperfusion injury
  • May start at time of injury
  • 1/3 of those who die after TBI talk/obey commands immediately after injury.
Molecular Pathophysiology of TBI

- Release of cellular mediators
  - Chemokines
    - Activate neutrophils
  - Adhesion molecules
    - P selectin
    - Intracellular adhesion molecules
    - Vascular adhesion molecules
  - Proinflammatory enzymes
    - TNF
    - Interleukin 1β
    - Interleukin 6 up-regulation
- Tissue damage
  - Direct: Neurotoxic mediators
  - Indirect: Nitric oxide, cytokines
Molecular Pathophysiology of TBI
Glutamate Excitotoxicity

- Indiscriminate release of glutamate occurs after TBI, resulting in calcium influx
- Activates MAP-kinase pathways that can trigger apoptosis
- Can activate nitric oxide synthase or xanthine oxidase – free radical production
- Can activate proteases and phospholipases
- Can accumulate in mitochondria
NMDA Receptors

• NMDA receptor subunits
  • NR1 - Required for function of ion channel, but not glutamate sensitive
  • NR2 – glutamate sensitive
    • 4 subtypes (A-D)
    • NR2A and NR2B found extensively in neocortex and hippocampus
    • NR2B predominates in neonatal period, but NR2A increases with development (closely tied to experience-dependent plasticity)

• The NR2A/NR2B ratio is highly correlated with neurodevelopmental maturation
Glutamate Excitotoxicity Sequelae

• After experimental TBI
  • Preferential down regulation of the NMDA receptor subunit NR2A occurs
    • Most prominent early after injury
    • Most profound in the ipsilateral hippocampus
    • Effect lasts for days (in rat model)
  • This may be the primary mechanism for deficits in experience-dependent plasticity

• Lead exposure results in decreased NR2A protein levels

Giza, C et al. *N-Methyl-D-Aspartate receptor subunit changes after traumatic injury to the developing brain.* J. Neurotrauma 2006; 23:(6) 950-961
Mental Break
# TBI Grading

<table>
<thead>
<tr>
<th>GCS</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13-15</td>
<td>9-12</td>
<td>&lt;9</td>
</tr>
<tr>
<td>TBI Grading</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>Loss of consciousness greater than 24 hours, with contusion, hematoma or skull fracture</td>
<td>Loss of consciousness more than 30 minutes and less than 24 hours, with or without skull fracture</td>
<td>Loss of consciousness less than 30 minutes and no skull fracture</td>
<td></td>
</tr>
</tbody>
</table>
# TBI Grading and Outcomes

<table>
<thead>
<tr>
<th></th>
<th>GCS</th>
<th>Permanent Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>13-15</td>
<td>10%</td>
</tr>
<tr>
<td>Moderate</td>
<td>9-12</td>
<td>66%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;9</td>
<td>100%</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Approx Time</td>
<td>2135 2150</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Resp</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Almost symmetrical</td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>Equal</td>
<td></td>
</tr>
<tr>
<td>GCS / ETCO₂</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Cap Refl</td>
<td>200/100</td>
<td></td>
</tr>
<tr>
<td>Pulse Ox</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Back</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Treatment / Procedure:
- Site: | Wireless Bluetooth | Procedure: | None |
- Date: | 2023-04-02 16:35 |
- Time: | 16:35 |
- Description: | None |

Hospital Communication:
- Room: | 1B |
- Phone: | 123-456-7890 |
- Notes: | None |

Miscellaneous Procedures:
- Block: | N/A |
- Block Date: | 2023-04-02 16:35 |
- Notes: | None |
### PHYSICAL EXAM

**BP:** 137/78  **HR:** 160  **RR:** 18  **O2 sat:** 98  **Temp:**

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Motor Response</th>
<th>Glasgow Coma Scale:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Spontaneously</td>
<td>6 Obey</td>
<td>3</td>
</tr>
<tr>
<td>3 To Speech</td>
<td>5 Localizes</td>
<td>4 Confused</td>
</tr>
<tr>
<td>2 To Pain</td>
<td>4 Withdraws</td>
<td>3 Inappropriate Words</td>
</tr>
<tr>
<td>1 None</td>
<td>3 Flexion</td>
<td>2 Inappropriate Sounds</td>
</tr>
<tr>
<td></td>
<td>2 Extends</td>
<td></td>
</tr>
</tbody>
</table>

### GLASGOW COMA SCALE

<table>
<thead>
<tr>
<th>Primary Survey</th>
<th>GLASGOW COMA SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eye Opening</td>
</tr>
<tr>
<td>Spontaneously</td>
<td>6 Obey</td>
</tr>
<tr>
<td>To Speech</td>
<td>5 Localizes</td>
</tr>
<tr>
<td>To Pain</td>
<td>4 Withdraws</td>
</tr>
<tr>
<td>None</td>
<td>3 Flexion</td>
</tr>
<tr>
<td></td>
<td>2 Extends</td>
</tr>
</tbody>
</table>

### Comments

- 15BH: 18H
- Zygoma (x)

**Secondary Survey Time:** 2208
Intensive Care Setting

• Hypotension
  • A single episode of hypotension during period from injury to resuscitation doubles mortality.
  • 90% of fatal head injuries have ischemic damage at autopsy.
  • Cerebral perfusion pressure (CPP = MAP – ICP) < 40 associated with increased mortality.

• Hypoxia
  • Early hypoxia (<90%) associated with poor outcome
  • May be marker of severity of injury

• Hyperglycemia
  • 50% of patients with severe TBI have blood glucose >200mg/dl
  • Peak glucose >200 in 1st 24hrs of admit associated with worse morbidity and mortality
  • Hypoglycemia less common (often a cause of LOC/ TBI)
Intensive Care Setting

• Hyper/hypocapnia
  • Hypercapnia = cerebral vasodilation = increased cerebral blood volume = increased intracranial pressure = decreased cerebral perfusion.
  • Aggressive hyperventilation (resulting in hypocapnia) has been detrimental.

• Hypothermia
  • Limited data
  • Hyperthermia associated with poor outcome.
  • IF done, should be performed early in course.

• Fluids
  • Important in maintaining blood pressure
  • NO evidence to support that giving increased volume results in cerebral edema
  • Hypertonic saline does not increase rate of bleeding.
  • Improved survival over those receiving Ringer’s lactate.
Intensive Care Setting

• ICP monitoring
  • Those with GCS < 8 have high risk of developing intracranial hypertension
  • ICP > 20mmHg associated with poor neurological outcome
  • Risk of uncal herniation

• Decompressive craniectomy
  • Children more likely to have diffuse cerebral edema
  • May be used in those with medically refractory intracranial hypertension
  • Child outcomes better than adults
Decompressive Craniectomy
Evidence

- Taylor, et al
- 27 patients (13 tx group) ages 1-15 yrs
- Sustained intracranial hypertension during the first day after admission
  - ICP 20–24 mmHg for 30 min, 25–29 mmHg for 10 min, 30 mmHg or more for 1 min) or had evidence of herniation
- 13 decompressive craniectomy less than 24 hrs
- 14 medical management
  - Reduced ICP in decompressive craniectomy group
  - Improved outcomes at 6 months

A randomized trial of very early decompressive craniectomy in children with traumatic brain injury and sustained intracranial hypertension
Craniectomy Evidence

Josan, et al

12 patients (6 tx group) 2 - 16 yrs old

Refractory elevated ICP in absence of mass lesion

Half medical management
Half early decompressive cranectomy

Marshall CT classification of severity

Improved Outcomes at 1 year in early decompression group despite worse Marshall scores

Table 2 Clinical profile of patients in the early craniectomy group

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Sex</th>
<th>GCS</th>
<th>Pupils</th>
<th>Marshall grade</th>
<th>Pre-operative ICP in mmHg</th>
<th>Non-operative measures</th>
<th>Time to surgery in hours</th>
<th>Surgery</th>
<th>Post-op ICP in mmHg</th>
<th>GOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>M</td>
<td>9</td>
<td>N</td>
<td>3</td>
<td>22</td>
<td>Hypothermia</td>
<td>3</td>
<td>Unilateral</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>11</td>
<td>N</td>
<td>3</td>
<td>29</td>
<td>Hypothermia</td>
<td>18</td>
<td>Bilateral</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>7</td>
<td>R fixed</td>
<td>3</td>
<td>28</td>
<td>EVD</td>
<td>10</td>
<td>Bilateral</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>8</td>
<td>N</td>
<td>3</td>
<td>35</td>
<td>–</td>
<td>2</td>
<td>Unilateral</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>3</td>
<td>Both fixed</td>
<td>3</td>
<td>36</td>
<td>EVD</td>
<td>3</td>
<td>Bilateral</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>3</td>
<td>N</td>
<td>3</td>
<td>34</td>
<td>(EDH evacuation)</td>
<td>6</td>
<td>Unilateral</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

N Normal sized and normal reaction
E extradural haematoma, SDH subdural haematoma

Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>GCS</th>
<th>Pupils</th>
<th>Marshall grade</th>
<th>Initial ICP in mmHg</th>
<th>Non-operative measures</th>
<th>GOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>M</td>
<td>4</td>
<td>L fixed</td>
<td>3</td>
<td>&gt;30</td>
<td>EVD &amp; thiopentone</td>
<td>1</td>
</tr>
<tr>
<td>11a</td>
<td>F</td>
<td>4</td>
<td>N</td>
<td>3</td>
<td>&gt;22, and 2 days later, &gt;40</td>
<td>Thiopentone &amp; hypothermia</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>7</td>
<td>L&gt;R reacting</td>
<td>1</td>
<td>&gt;22</td>
<td>EVD</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>9</td>
<td>N</td>
<td>2</td>
<td>&gt;22</td>
<td>EVD, thiopentone &amp; hypothermia</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>8</td>
<td>N</td>
<td>2</td>
<td>&gt;20, and 2 days later, &gt;38</td>
<td>Hypothermia</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>4</td>
<td>N</td>
<td>2</td>
<td>&gt;20</td>
<td>EVD</td>
<td>5</td>
</tr>
</tbody>
</table>

This patient underwent delayed decompressive craniectomy at 9 days

N Normal size and normal reaction
Pharmacologic Interventions

- **Mannitol**
  - Cornerstone of hyperosmolar therapy for elevated ICP
  - Not subjected to randomized studies, etc.
  - Used by > 70% PICUs
  - Mechanisms of action
    - **Rapidly** reduces blood viscosity which reduces blood vessel diameter, cerebral blood volume and subsequently ICP
    - **Slowly**, has osmotic effect on parenchyma to move water to circulation
  - Dose: 0.25g/kg – 1g/kg

- **Steroids**
  - No evidence to suggest improvement in outcome
  - Some evidence for worse outcome in those treated with steroids
ICU Care

Controversies in TBI

• Neuroplasticity

  • Kennard Principle: “the young brain is more capable of reorganization than the mature brain.”

  • Margaret Kennard, 1936. Inflicted cortical lesions in infant and adult monkeys and found that behavioral consequences less severe in infants than compared with adults.

• 2 key components
  • Location of injury
    • Motor cortex has largest potential for post-lesional plasticity
    • Prefrontal cortex lesion more likely to have long term consequence
  • Timing of injury
    • Most detrimental: 1 month (massive cellular migration)
    • Least detrimental 1 month to 2 years (unless diffuse)
Controversies in TBI

• Neuroimaging

  • CTH exposes children to radiation
    • Children are radiosensitive due to rapidly dividing cells associated with growth
    • Peds adjusted CTH = 30 millisieverts
    • Normal CTH = 60 millisieverts
    • 200-600 times as much radiation as an AP chest xray
    • Lifetime risk of FATAL cancer in infant 1/2000 scans
    • Lifetime risk of FATAL cancer in older child 1/5000 scans

• Incidence of skull fracture or intracranial injury in all children is < 2%

• Incidence of skull fracture or intracranial injury in kids less than 2 years is 11%
CT scanning for TBI
CT scanning for TBI
CT scanning for TBI

- Kupperman, et al. September 15, 2009
- 42,412 children enrolled at 25 emergency rooms (June 2004-March 2006)

Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study

- > 2yrs (25283 derivation/6411 validation
- 14,969 CT scans
CT for Children after TBI

- Criteria for children < 2 yrs.
  - Negative predictive value: 100%
  - Sensitivity: 100%
- Criteria for children > 2 yrs.
  - Negative predictive value: 99.95%
  - Sensitivity: 96.8%
Sequelae of Non-accidental Trauma

Seven month male with sudden loss of consciousness.
Inflicted trauma later confirmed.
Sequelaes of Non-accidental Trauma

Day 2
Sequela of Non-accidental Trauma

4 months after injury
Sequelae of TBI

• Day 1
TBI Sequelae

- Day 3
TBI Sequelae
Question

What was this patient’s outcome?

- A. Death
- B. Severe hemiparesis and language impairment
- C. Persistent vegetative state
- D. Ambulatory with cognitive problems and epilepsy
- E. Normal
One year later
Posttraumatic Seizures

- Immediate
  - Within 5 minutes of TBI (within 24 hrs)
  - Does not represent epilepsy
  - Should be considered response to head injury – i.e. provoked

- Early
  - Within 7 days of TBI

- Late
  - After 7 days of TBI

- Risk factors
  - Surgically evacuated SDH
  - Intracerebral hematoma
  - GCS < 8
  - Depressed skull fracture
  - Penetrating injury
  - Parietal lesions on CT scan
Antiepileptic Drugs for Posttraumatic Seizures

Bernard S. Chang and Daniel H. Lowenstein
Neurology 2003;60;10-16
Antiepileptic Drugs for Posttraumatic Seizures

• Prophylactic antiepileptic drug (phenytoin) treatment reduces the risk of early (within 7 days) posttraumatic seizures.

• Prophylactic antiepileptic drug treatment (phenytoin) does not reduce the risk of late (greater than 7 days) posttraumatic seizures.

“Further studies addressing milder forms of TBI, the use of newer AEDs, the utility of EEG, and the applicability of these findings to children are recommended.”
Antiepileptic Drugs for Posttraumatic Seizures

- 103 (69) Children < 16 yrs
- TBI with GCS < 10
- 46 received phenytoin
- 56 placebo
- 7% had seizure in phenytoin group
- 5% had seizure in placebo group

The rate of early posttraumatic seizures in children may be much lower than previously reported. Phenytoin did not substantially reduce that rate.

A bone of the skull of a twelve-year old youth had been broken and depressed by a fall and had by negligence not been restored. The brain was therefore hindered in its growth, since the injured bone itself could not grow so as to become able to hold a larger brain. Consequently in his eighteenth year the youth suffered from epilepsy because of the oppression of the brain. He was, however, cured by perforation of the depressed bone, for thus the oppression of the brain was removed. (Temkin, 1945)
Post traumatic Epilepsy

- Accounts for 20% of all symptomatic epilepsy
- Most common cause of epilepsy in young adults
- Risk of developing epilepsy
  - Mild TBI: 1.5 fold increased risk
  - Moderate TBI: 4 fold increased risk
  - Severe TBI: 30 fold increased risk
Posttraumatic Epilepsy

- Risk Factors
  - Injury characteristics
    - Penetrating injury
    - Depressed skull fracture
  - Patient
    - Age > 15 years
    - EtOH abuse
    - Family history of PTE
    - Depression – 2X risk
  - Timing
    - Highest within 2 years
Posttraumatic Epilepsy

- Persistence
  - 50% stop having seizures between 5-10 years with or without treatment

- Mortality
  - 3X higher than non-PTE
  - Average 15 years younger than non-PTE
  - M>F
  - More likely to die from a new TBI
Conclusion

- Traumatic brain injury is the leading cause of morbidity and mortality in children

- Initial management of moderate to severe brain injury should focus on maintaining oxygenation, blood pressure, normoglycemia and preventing intracranial hypertension

- Posttraumatic seizures prophylaxis in children is unnecessary

- Posttraumatic Epilepsy rates in children are lower than in adults, though injury and patient risk factors are more predictive

- Mortality rates for PTE patients are higher than that of other patients with epilepsy