Diagnostic and Prognostic Advances in Pediatric Mild Traumatic Brain Injury

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CME Disclosure Statement

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• I do not intend to discuss an unapproved or investigative use of a commercial product/device in my presentation.
Learning Objectives

1. Implement current diagnostic and prognostic methods for children with mild TBI.

2. Understand how serum biomarkers aid in the diagnosis and prognosis of children with mild TBI.

3. Appreciate advanced neuroimaging as a diagnostic and prognostic tool for children with mild TBI.
Case

9 year old boy is playing hockey. Helmeted. Is chasing after the puck, gets tripped (of course accidently) and then gets pile driven into the boards by a much larger 10 year old. He appears unresponsive for about 1 minute, then he starts to cry. He is unable to get up, and then is helped off the ice. He is dazed and confused for about 5 minutes. His parents bring him into ED.

Parents ask:
Does he have a brain injury?
When can he go back into the game?
Primary Injury

- **“Focal” injuries**
  - Direct mechanical damage
  - Impact
  - Acceleration, deceleration
  - Results:
    - Coup/counter coup
    - Hemorrhage/infarction
    - Rapid oncotic injury $\rightarrow$ cell death by necrosis

- **“Diffuse” injuries**
  - Rotational forces critical
  - Acceleration, deceleration
  - Results:
    - Axonal stretch $\rightarrow$ axotomy
    - Primary axotomy
    - Microhemorrhages
Secondary Injury

- **Stretch**
  - Mechanoreceptor dysregulation
  - Release of glutamate → receptors

- **Acidify**
  - Voltage dependent receptor activation, ↓ATP
  - Ionic flux (intercellular ↑Ca2+, ↑Na+)

- **Destroy**
  - Activation of cysteine proteolytic enzymes

- **Death**
  - Neurofilament sidearms loss and compaction
  - Cytoskeletal collapse
  - Necrosis, apoptosis
Current ED Evaluation

- Mechanism of Injury
- Historical Factors
  - Loss of consciousness
  - Vomiting
  - Amnesia
  - Seizures
  - Headache
- Physical Exam
  - Glasgow Coma Scale
  - Neurologic exam
  - Scalp hematoma
  - Skull fracture
  - ?Balance
  - ?Visual tracking

Decision Rules

Head CT

DISABILITY

Serum Markers?

Neuroimaging Tools?

Brain Activity?
Clinical Presentation: Diagnostic Tool
PECARN Neuroimaging Decision Rules

Child is at very low risk of clinically important TBI and CT is not needed if all of the following are met:

### Age younger than 2 years
- GCS = 15 and no other signs of abnormal mental status
- No loss of consciousness (LOC) or LOC < 5 seconds
- No temporal, parietal, or occipital scalp hematoma
- No severe mechanism of injury
- No palpable / suspected skull fx
- Acting normally per parent

### Age 2-18 years
- GCS = 15 and no other signs of abnormal mental status
- No LOC
- No history of emesis
- No severe mechanism of injury
- No signs of basilar skull fx
- No severe headache

# PECARN Neuroimaging Rule

## Test Characteristics

<table>
<thead>
<tr>
<th>Age: &lt; 2 years</th>
<th>Derivation</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction Rule Sensitivity (95% CI)</td>
<td>98.6% (92.6-99.97)</td>
<td>100% (86.3 – 100)</td>
</tr>
<tr>
<td>Prediction Rule Specificity (95% CI)</td>
<td>53.7% (52.6-54.8)</td>
<td>53.7% (51.6 – 55.8)</td>
</tr>
<tr>
<td>Negative Predictive Value (95% CI)</td>
<td>99.9% (99.88 – 99.999)</td>
<td>100% (99.7 – 100)</td>
</tr>
<tr>
<td>Positive Predictive Value (95% CI)</td>
<td>1.8% (1.4 – 2.3)</td>
<td>2.4% (1.6 – 3.5)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Age: 2 – 18 years</th>
<th>Derivation</th>
<th>Validation</th>
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<tr>
<td>Prediction Rule Sensitivity (95% CI)</td>
<td>96.7% (93.4 – 98.7)</td>
<td>96.8% (89.0 – 99.6)</td>
</tr>
<tr>
<td>Prediction Rule Specificity (95% CI)</td>
<td>58.5% (57.9 – 59.1)</td>
<td>59.8% (58.6 – 61.0)</td>
</tr>
<tr>
<td>Negative Predictive Value (95% CI)</td>
<td>99.95% (99.90 – 99.98)</td>
<td>99.95% (99.81 – 99.99)</td>
</tr>
<tr>
<td>Positive Predictive Value (95% CI)</td>
<td>2.0% (1.7 – 2.2)</td>
<td>2.3% (1.8 – 3.0)</td>
</tr>
</tbody>
</table>
A

GCS=14 or other signs of altered mental status†, or palpable skull fracture

Yes

CT recommended

13.9% of population
4.4% risk of ciTBI

No

Occipital or parietal or temporal scalp haematoma, or history of LOC ≥ 5 s, or severe mechanism of injury‡, or not acting normally per parent

Yes

Observation versus CT on the basis of other clinical factors including:
- Physician experience
- Multiple versus isolated§ findings
- Worsening symptoms or signs after emergency department observation
- Age < 3 months
- Parental preference

32.6% of population
0.9% risk of ciTBI

No

53.5% of population
<0.02% risk of ciTBI

CT not recommended¶
2-18 years

**B**

- **GCS = 14 or other signs of altered mental status†, or signs of basilar skull fracture**
  - Yes
    - 14.0% of population
    - 4.3% risk of ciTBI
    - CT recommended
  - No
    - 58.3% of population
    - <0.05% risk of ciTBI
    - CT not recommended‡

- History of LOC, or history of vomiting, or severe mechanism of injury‡, or severe headache
  - Yes
    - 27.7% of population
    - 0.9% risk of ciTBI
    - Observation versus CT on the basis of other clinical factors including:
      - Physician experience
      - Multiple versus isolated§ findings
      - Worsening symptoms or signs after emergency department observation
      - Parental preference
  - No
    - 58.3% of population
    - <0.05% risk of ciTBI
    - CT not recommended‡
Those in the very low-risk group, for whom CT scans could routinely be obviated, accounted for 25% of CTs obtained in children <2 years and 20% of CTs in those 2 to 18 years.

https://vimeo.com/36792246
Disability

• Up to 50% of children will have sequelae
  – > 80% have resolution within 7-10 days
  – ?? 10-30% have persistent symptoms weeks to years
  – Longer recovery

• Equivocal long term deficits
  – ? ADHD, visual deficits, reading impairment, memory, psychomotor speed, language
Post-Concussion Syndrome (PCS)

- **Symptoms:**
  - Chronic Headache
  - Light/Noise sensitivity
  - Nausea
  - Chronic Fatigue
  - Dizziness
- **Behavioral Deficits**
  - Personality Changes
  - Depression
  - Anxiety
  - ADHD
- **Sleep Deficits**
- **Cognitive Deficits**
- **Academic Difficulties**
  - Absenteeism
  - Concentration
- **Chronic Traumatic Encephalopathy?**
Rochester mTBI Cohort

Mild TBI
2-18 Years Old
n=620

3 month F/U
Completed
n=502

Lost to F/U
n=118

PCS
n=150

No PCS
n=352

30%

Days of School Missed

7.9

2.3

JAMA Pediatrics, 2013
Diagnostic and Prognostic Tools

Clinical Presentation
- Demographics, Symptoms, Mechanism, Injury
- Visual tracking, Postural stability

Neuroimaging
- CT, MRI, DTI, PET, SPECT

Serum Markers
- Known: S100B, NSE, GFAP, SDP, UCHL-1, cleaved-tau, MBB
- Undiscovered
### Risk Factors for More Complicated Recovery

<table>
<thead>
<tr>
<th>Factor</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Teenagers</td>
<td>Headache</td>
</tr>
<tr>
<td>Gender: Females</td>
<td>Amnesia</td>
</tr>
<tr>
<td>Migraine history</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Learning disability</td>
<td>Fogginess</td>
</tr>
<tr>
<td>Repetitive concussion</td>
<td>Admission</td>
</tr>
<tr>
<td>LOC</td>
<td>Nausea</td>
</tr>
<tr>
<td>Motor vehicle related</td>
<td>Disorientation</td>
</tr>
<tr>
<td>&gt;= 4 symptoms</td>
<td>CT abnormalities</td>
</tr>
</tbody>
</table>
Why search for Alternative Tools?

- Identifying neurologic injury after TBI problematic
- Clinical variables and CT scan are poor proxies for severity and sequelae
- Prevents
  - Accurate diagnosis of brain injury
  - Accurate prediction of outcome
  - ID of subgroups most likely to respond to treatment
Discovering Markers

Events post-TBI
Ideal Marker

- Brain origin
- Elevated soon after TBI
- Correlate with injury severity
- Correlate with other measures of injury
- Sensitive to detect mTBI
- Predict outcome
- Predict therapy efficacy
1. Oligodendrocytes
2. Neuron axon
3. Neuron cell body
4. Myelin
5. Microglia
6. Astrocytes
7. Synaptic junction
8. Blood vessels
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Injury Detected</th>
<th>Correlation Diagnostic</th>
<th>Correlation Prognostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100B</td>
<td>Astrocytes and blood brain barrier</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Glial Fibrillary Acidic Protein</td>
<td>Astrocytes</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Ubiquitin C-terminal hydrolase</td>
<td>Neuronal</td>
<td>Poor/Good</td>
<td>Good</td>
</tr>
<tr>
<td>Neuron-Specific Enolase</td>
<td>Neuronal</td>
<td>Poor</td>
<td>Fair</td>
</tr>
<tr>
<td>Myelin Basic Protein</td>
<td>Oligodendrocytes</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Cleaved-Tau</td>
<td>Axonal</td>
<td>Fair</td>
<td>Fair</td>
</tr>
<tr>
<td>Neurofilament Heavy Chain</td>
<td>Neuronal</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Spectrin Breakdown Products</td>
<td>Neuronal necrosis/apoptosis</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>
S100B

- Best studied marker (>3000 patients)
- Found in astrocytes
- Minute amounts in adipocytes, chondrocytes, melanocytes and epidermal cells
- Peaks 1-2 hours
S100B and CT Scan

- More sensitive than specific predictor of abnormal brain CT

<table>
<thead>
<tr>
<th></th>
<th>Sen</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild TBI</td>
<td>90-100%</td>
<td>40-65%</td>
</tr>
<tr>
<td>Sev TBI</td>
<td>100%</td>
<td>NR</td>
</tr>
</tbody>
</table>

- False negatives are rare
- Routine S100b could reduce CT scanning for mTBI by 30%
- Clinically in use in Europe in adults
S100B: Diagnostic Tool

- N=109
- Head CT
- S100B

GFAB as a Diagnostic Tool
(glial fibrillary acidic protein breakdown products)

- **Adults**  Papa, Ann Emerg Med, 2012
  - Correlates with GCS, CT lesions, ciTBI
  - Highly specific for brain tissue

- **Pediatrics** Babcock, AAP, 2013
  - 23 cases with mTBI and 20 ortho controls
  - Cases had a significantly higher mean GFAP levels than controls (0.072±0.087 vs. 0.014±0.022 ng/mL, p=0.007).
  - GFAP did correlate with PECARN risk stratification categories (R^2=0.44, p=0.0005).
# Advanced Neuroimaging

<table>
<thead>
<tr>
<th>Modality</th>
<th>How is Brain Injury Detected</th>
<th>Frequency of Detection of INJURY in mTBI</th>
<th>Correlation with Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan</td>
<td>Hemorrhage Some edema</td>
<td>3-7</td>
<td>Weak</td>
</tr>
<tr>
<td>SPECT</td>
<td>↓ uptake of radiolabeled technetium-99m (↓ regional cerebral blood flow)</td>
<td>59-87</td>
<td>Moderate</td>
</tr>
<tr>
<td>PET</td>
<td>Initially ↑ followed by ↓ uptake of radiolabeled glucose and O2 (↑ then ↓ neuronal metabolism)</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
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## Advanced Neuroimaging

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<thead>
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<th>How is Brain Injury Detected</th>
<th>Frequency of Detection in mTBI</th>
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</tr>
</thead>
<tbody>
<tr>
<td>MR T1/T2</td>
<td>White matter lesions&lt;br&gt;Small hemorrhages&lt;br&gt;Small contusion</td>
<td>10-57</td>
<td>Moderate</td>
</tr>
<tr>
<td>MR Spectroscopy</td>
<td>Spectroscopic peaks show&lt;br&gt;↑NAA, ↓choline</td>
<td>Unclear</td>
<td>Limited data</td>
</tr>
<tr>
<td>Functional MRI</td>
<td>↓ ratio oxyHb to deoxyHb&lt;br&gt;(↑ O2 utilization)</td>
<td>≥50%</td>
<td>Good</td>
</tr>
<tr>
<td>SWI</td>
<td>Deoxygenated blood products&lt;br&gt;Punctate hemorrhages</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Phase Contrast Angiography</td>
<td>Cerebral blood flow&lt;br&gt;(Maugans, Pediatrics 2012)</td>
<td>reduction in CBF</td>
<td>? none</td>
</tr>
</tbody>
</table>
Diffusion of water preferentially tracts parallel to axons in the white matter (WM)

Diffusion tensor imaging (DTI) measures the preferred direction of water in WM
Approximately 50 published DTI studies on TBI in children

7 on mTBI, 4 during the acute time period

Two typical times post-injury (within 7 days of injury or greater than 6 months);

Small samples = 6 < N < 20

Severe TBI
  - Reduced FA
    - Injury severity
    - Functional outcomes
Select White Matter Regions that Displayed Differences in FA between mTBI cases and OI controls

Blue Shaded White Matter Regions
mTBI cases > OI Controls
p <0.05, corrected

Left Middle Temporal Gyrus WM
Left Superior Temporal Gyrus WM
Left Anterior Corona Radiata
Right Superior Longitudinal Fasciculus

Babcock, 2013

<table>
<thead>
<tr>
<th></th>
<th>mTBI Cases</th>
<th>OI Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>n=23</td>
<td>n=20</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>13.2 ± 1.8 yrs</td>
<td>12.7 ± 1.5 yrs</td>
</tr>
<tr>
<td>Hours to Scan</td>
<td>46.2 ± 17.1</td>
<td>51.5 ± 19.5</td>
</tr>
</tbody>
</table>
Conclusions

- Water diffusion has increased directionality and is more parallel to the axon in multiple areas of the brain 48 hours after a single mTBI in children.

- This suggests that diffuse axonal swelling occurs within the first 48 hours after a single mTBI in children.
Therapy

• No proven medical interventions
  – Further research is needed

• Systemic Review -- 17 RCT
  – Only 3 involved children
  – 3 anticipatory guidance: all +
  – 3 cognitive behavioral therapy: all+
  – 2 mindful based rx / relaxation: +/-
Will a pill cure?

- **Sleep**: melatonin, trazadone
- **Somatic /headaches**:  
  - Short term: ibuprofen, tylenol
  - Longer term: amitriptyline, β-Blockers, calcium channel blockers, valproic acid, topiramate, triptans, dihydroergotamine, gabapentin
- **Emotional / depression**: tricyclic antidepressants, serotonin reuptake inhibitors
- **Cognitive**: methyphenidate, amantadine, (doenpezil, rivastigmine, cytidine diphosphoryl choline, fluoxetine, sertraline, pramiracetam, bromocriptine, and atomoxetine)
Recent Pilot Studies

- Hypertonic saline? (Lumba, 2013)
- Cognitive rest: Is too much a bad thing? (Thomas, 2013)
- Sub-threshold exercise therapy? (Kurowski, 2014)
- Online education / cognitive behavior therapy? (Babcock, 2014)
Summary

• Clinical Presentation
  – CT decision rules using clinical presentation help in diagnosis of clinically important TBI
  – Certain symptoms aid in prognosis

• Serum Markers
  – S100B is a good diagnostic tool but poor prognostic tool
  – GFAP shows promise as a diagnostic marker
Summary

• Neuroimaging
  – CT can diagnose clinically important TBI
  – MRI more sensitive diagnostic and prognostic tool
  – DTI measures anisotropic water diffusion in brain white matter
    • May be a very useful in the diagnosis
    • Little evidence about changes correlating to prognosis

• Therapy
  – Anticipatory guidance
  – Cognitive behavioral therapy
  – Limited investigation