The incidence of post-traumatic epilepsy after TBI: a TRACK-TBI study

18TH ANNUAL NEURO-TRAUMA SYMPOSIUM
Monday, December 2, 2019
John F. Burke, MD, PhD
Traumatic Brain Injury: 2019

A Complex and Heterogeneous Disease

Clinical Assessment
- GCS (Glasgow Coma Scale)
  - Mild
  - Severe
  - Concussion

Outcome
- GOS (Glasgow Outcome Scale)
  - Death
  - Vegetative
  - Good Recovery

Sequelae
- 1. Incidence
- 2. Risk-Factors
- 3. Outcome

Endpoints Development

A Collaborative for Advancing Diagnosis and Treatment of TBI
Post-traumatic Epilepsy: Outcome

Why is it important to diagnose and treat PTE?

- Patients with TBI and PTE perform worse across several performance and clinical metrics:
  - Independence
  - Cognitive Assessments
  - Illegal drug use
  - Satisfaction with life

- Patients with PTE are significantly more disabled, less independent, and prone to higher rates of mental illness (depressions, addiction, etc)

- **Bottom-Line**: Preventing PTE will improve outcomes following TBI.

### Table 4

<table>
<thead>
<tr>
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<th>Year 5</th>
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<tbody>
<tr>
<td></td>
<td>LPTS</td>
</tr>
<tr>
<td>DRS score</td>
<td>3.0 ± 2.8</td>
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<tr>
<td>FIM Cognitive subscale</td>
<td>29.7 ± 5.2</td>
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<tr>
<td>FIM Motor subscale score</td>
<td>83.7 ± 12.5</td>
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<tr>
<td>FIM Total score</td>
<td>114.1 ± 15.7</td>
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<tr>
<td>SRS score</td>
<td></td>
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<tr>
<td>Independent</td>
<td>29/56 (52%)</td>
</tr>
<tr>
<td>Unsupervised overnight</td>
<td>18/56 (32%)</td>
</tr>
<tr>
<td>Supervised overnight</td>
<td>9/56 (16%)</td>
</tr>
<tr>
<td>Illegal drug use</td>
<td>16/79 (20%)</td>
</tr>
<tr>
<td>Arrests d</td>
<td>5/80 (6%)</td>
</tr>
<tr>
<td>Attempted suicide d</td>
<td>2/73 (3%)</td>
</tr>
<tr>
<td>Psychiatric hospitalization d</td>
<td>3/73 (4%)</td>
</tr>
<tr>
<td>Satisfaction with sexual activity d</td>
<td>23/29 (79%)</td>
</tr>
<tr>
<td>SWLS score a</td>
<td>17.4 ± 8.2</td>
</tr>
</tbody>
</table>

**Bushnik, et al (2012), J Head Tr. Rehab**

How likely is PTE after TBI?
Post-traumatic Epilepsy: Incidence

Why is it important to know the incidence of PTE?
- 2.8 million TBI/yr in US
- 20% symptomatic epilepsy from trauma
- Understanding the incidence, risk factors, and mechanisms for PTE has major public health implications

What do we know?
- Best incidence data over 20+ yrs old.
- Relation between injury severity and PTE
  - “mild TBI” incidence 0.7% at 5 years
  - PTE incidence goes up linearly to 30 yrs
    - 2.1% at 30 years

What is our approach?

TRACK TBI Goals

1. Improve TBI diagnosis and classification/taxonomy
2. Improve TBI outcome assessment
3. Identify the health and economic impact of Mild TBI
4. Create a “Information Commons” to promote collaboration and acceleration of TBI research

PTE Study Goals

1. Sequelae: who develops PTE?
2. How does PTE affect outcome?
3. PTE as a cause of seizures.
4. Predictive models/risk calculators of developing PTE at time of injury.

Prospective longitudinal Precision Medicine Study
- 3000 subjects, including Controls
-Across the spectrum from concussion to coma
Methods: NINDS PTE screening questionnaire

- 2,698 TRACK TBI patients

- At 6- and 12-month follow up, patients given an epilepsy screening questionnaire

- Based on results of four “trigger” questions, patients were asked additional questions to verify PTE cases.

- Trigger questions based on NINDS PTE screening questionnaire
Results: Response to “triggers”

- Detecting heterogeneous pathology
  - concussion syndrome
  - nausea/vomiting, vertigo manifesting as “unusual attacks”
  - Sensitive not specific
- Increased incidence at 6 months
  - not expected based on Anneger’s data
  - possible increased vigilance
- Far above baseline epilepsy rate
  - also should the cohort of patients who seized and fell
Results: PTE across TBI spectrum

- full incidence of PTE depends on the severity of presentation
- dramatic increase in PTE risk in GCS 3 - 8
- higher rate at 12 months indicates increasing seizure development
- GCS 13-15
  - non-trivial (~1%)
  - What is combined rate of PTE for GCS 13-15 cohort?
Results: PTE after TBI (GCS 13-15)

- Seizure in less severe TBI (GCS 13-15) is 1.4% at 12 months

- Higher than the rate quoted in Anneger’s et al (largest retrospective study to date, 0.7%)

- Indicates less clinically severe TBI confers an additional seizure risk even at 12 months
Prediction I

- Ultimate goal is to predict who is at risk of PTE, and enter them into an aggressive seizure monitoring/treatment protocol

- One strategy is to use all clinical variables in a multivariate classifier, to maximize prediction accuracy.
  - Very good results
  - prediction > chance (0.75 > 0.5)

- When we looks at the weights initial GCS is the most predictive variable
  - Caution: What is driving this effect?
Prediction II

- First results suggest GCS is best predictor
  - Double the risk of PTE at 12 months when GCS < 12
  - 10 x the risk for all GCS <= 8
  - **Simple rule:** all patients with GCS 12 or less should be monitored closely with intensive PTE screening

- GCS 13-15: where prediction algorithms are needed the most
  - Large number of patients, few get PTE
  - More challenging to predict
    - AUC = 0.555 is still significantly > 0.5
  - Future classifiers should incorporate use of serum biomarkers, imaging, clinical data: **Precision medicine approach**
Three major limitations in this analysis

1. Follow-up
   - Anneger’s data suggest that there is a linear increase in PTE rate up to 30 years
   - 12 month follow-up means we are misclassifying PTE patients

2. Diagnosis
   - Epilepsy should be diagnosed by an epileptologist
   - We need more accurate seizure work-up and assessments
Overview of TRACK-TBI LONG

N = 3300 TBI and Control Subjects

AIM 1 | Telephonic long-term follow up/screening and consent for brain donation

AIM 2 | Imaging biomarkers

AIM 3 | Biofluid biomarkers

TRACK-TBI EPI

- All subjects in TRACK-TBI
  - contacted via phone 5 years after index TBI
- Subjects with positive NINDS screen → evaluated in clinic
  - EEG/epileptologist evaluation
  - repeat psychological evaluation
  - MRI/blood biomarker evaluation
Limitations

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3. Prediction models
   - Ripe for predictive analytic approach
   - Blood biomarkers, imaging, clinical, genome…
Conclusions and next steps

PTE is a common complication of TBI and cause of epilepsy

Development of effective anti-epileptogenic treatments will require a sophisticated understanding of the clinical, imaging, neurophysiologic, and molecular features of epileptogenicity resulting from TBI

A Precision Medicine approach to PTE
- Clinical risk factors
- Imaging and blood-based biomarkers
- Genetics
Thank you

Acknowledgements
- Dr. Geoffrey Manley, Dr. Michael Huang, Dr. Phiroz Tarapore, Dr. Sanjay Dhall

TRACK-TBI Team, including
- Dr. Ramon Diaz-Arrastia
- Dr. Nancy Temkin
- Dr. Dan Lowenstein
- Brian Fabian
- Sabrina Taylor

SFGH BASIC Team, including
- Lawrence Chyall, MS, RN
- Julia Thompson Gallego, MS, ACNP-BC
- Daniel McGuire, MS, ACNP-BC
- Amy Winkelman, MSN, ACNP-BC
- Twyila Lay, MS, ACNP-BC
- Among others!
References


2. Lowenstein DH: Epilepsy after head injury: An overview. Epilepsia 50:4–9, 2009