Occurrence and Risk Factors for Post-traumatic Epilepsy in Civilian Populations

December 2, 2012

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GH Sergievsky Center
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## Disclosure

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Learning Objectives

• To understand the proportion of epilepsy due to traumatic brain injury (TBI) in incident and prevalent cohorts.

• To understand the cumulative risk for epilepsy by TBI severity in civilian populations

• To understand risk factors for post-traumatic epilepsy in civilian populations and risk for specific seizure types
Minimal criteria for brain injury

- Loss of consciousness (even seconds)
- Focal neurologic deficit
  - e.g... hemiparesis, aphasia
- Injury on CT or MRI Imaging
  (contusion, intracranial hematoma)
Sequelae of Traumatic Brain Injury

• Post concussion syndrome

• Focal neurological deficit

• Cognitive impairment

• Post-traumatic epilepsy
Incidence and distribution of Traumatic Brain Injury

- 180/100,000 to 281/100,000
- Incidence peaks in young adults and in the elderly
- TBI is 1.8 to 2.8 fold more common in males
- Falls and transportation-related accidents predominate, accounting for 63% to 79% of injuries.
Proportion of incident epilepsy by etiology, Rochester, MN 1935-84

- Unknown/genetic: 65%
- Vascular: 10%
- Congenital: 8%
- Trauma: 6%
- Tumor: 4%
- Degenerative: 4%
- Infection: 3%

Hauser et al. Epilepsia 1993;34:453-458
Proportion of prevalent epilepsy by etiology, Rochester, MN 1940-1980

Cumulative incidence of unprovoked seizure by TBI severity

![Graph showing the cumulative incidence of unprovoked seizures by TBI severity over time. The graph includes data for mild, moderate, and severe injuries, as well as the general population. The table below the graph provides the number of patients and SMR (standardized mortality ratio) for each injury severity level.]

- **Number of Patients**
  - Mild injury: 2758, 1751, 1191
  - Moderate injury: 1455, 934, 660
  - Severe injury: 328, 181, 136
  - Total: 4541, 2866, 1987

- **SMR**
  - Mild injury: 1.5
  - Moderate injury: 2.9
  - Severe injury: 17.0

Late Seizures

![Graph showing cumulative incidence of seizures over months from injury](image)

Temkin et al. Epilepsia 2003;44:18-20
Relative Risk for epilepsy by TBI severity in children

Figure: Relative risk of epilepsy after brain injury in Denmark (1977-2002)

Christensen et al. Lancet 2009;373:1105-1110
Risk factors for unprovoked seizures after civilian TBI

- Brain contusion or SDH
- Brain contusion only
- SDH only
- Linear fx & >5 yrs or depressed fx
- LOC/PTA >24 hrs
- Age >65 yrs

Rate Ratio

TBI and risk for different seizure types before age 35 years

Impact on Clinical Care and Practice

• The increased risk for epilepsy is limited to moderate and severe civilian TBI, which comprises ~5% of all incident and all prevalent epilepsy

• In people under 35 years of age, TBI increases the risk for GTCS and for CPS, but not for absence seizures

• Risk factors for epilepsy after TBI include brain contusion, SDH, linear or depressed fracture, LOC/PTA >24 hours, and age ≥65 years

• The risk for epilepsy after civilian TBI is greatest in the first two years after TBI in most studies except Rochester where the greatest risk for severe TBI persists for 10 years
Epidemiology of TBI: Risk Factors and Natural History

December 2, 2012

Susan T. Herman, MD
Beth Israel Deaconess Medical Center
Harvard Medical School
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Learning Objectives

• Identify common risk factors for post-traumatic epilepsy
• Explore the relationship between early and late post-traumatic seizures
• Describe the natural history of post-traumatic epilepsy and risk of intractable epilepsy
Epileptogenesis

Initial Precipitating Injury

Latent period

Spontaneous Late Seizures

Age

Genetic factors

Epilepsy

Recurrent in >80%

Acute Symptomatic Seizures

Epileptogenesis?
Acute Symptomatic Seizures

- Provoked seizures
- First 1-2 weeks after brain injury
- Marker of severity of underlying disorder

Acute Symptomatic Seizures

• Associated with development of epilepsy
• Late seizures occur in 47% of patients with clinical AS
• AS are independent predictor (OR 2.84) for development of late seizures
Seizure Prevention Trials after Traumatic Brain Injury

Temkin et al., J Neurosurg 1999;91:593-600
Electrographic Seizures in TBI

• Seizures in critically ill patients often subclinical
  – Paralytic or sedative agents
  – Underlying neurological deficit
  – Administration of AEDs

• Prospective study of 91 patients with severe TBI
  – EEG monitoring for 7-10 days
  – All patients received prophylactic phenytoin
  – 22% had seizures
    • 57% only subclinical
  – 6/6 patients with status epilepticus died

Vespa et al., J Neurosurg, 1999;97:750-760
Early PTS and Epilepsy

• Retrospective analysis
• 140 patients with moderate to severe TBI, CEEG
  – 16 patients volumetric MRI, acute and 6 months
  – 6 patients with early seizures, 10 age- and GCS-matched patients with TBI, no seizures
  – Patients with seizures showed greater hippocampal atrophy (21 +/- 9 vs 12 +/- 6%, p = 0.017), especially ipsilateral to the electrographic seizure focus

Vespa PM et al. Neurology 2010;75:792-798
Interictal Epileptiform Discharges

• Animal model of TBI
  – IEDs and brief electrographic Sz precede clinical seizures

• Inadequately studied in humans
  – Non-standardized timing and methods for EEG
  – Most utilize routine EEG
    • IEDs are rare in adults, even those with acquired brain injuries
  – Presence of IEDs +/- focal slowing at 1 month associated with 3.5-fold higher risk of developing late seizures (n=137, 18 with epilepsy

Natural History of PTE

- 86% of patients with 1 late unprovoked post-traumatic seizure experience a second seizure within 2 years \(^1\)
- 25-40% seizure remission rate in non-penetrating TBI \(^2\)
- 39 selected adult patients (25 male) with moderate TBI \(^3\)
  - 36% required more than 1 AED trial
  - 8% failed multiple AEDs
- TBI associated with increased risk of refractory epilepsy \(^4\)
- 27% of patients with TBI and PTE died at 8 to 15 years after injury vs. 10% of matched TBI-only patients \(^5\)

Predictors of Intractable Epilepsy

Odds ratio, refractory vs. controlled, multivariate logistic regression

- Recreational drug use: 4.93
- Previous seizures: 3.26
- Age < 10 at last seizure: 2.77
- Traumatic brain injury: 2.23
- Psychiatric comorbidity: 2.17
- Family history: 1.99
- Neurological deficit: 1.77
- Sex: male gender: 1.13
- Age > 1 y since seizure: 1.08
- Maternal medication:

Summary

• Early seizures are associated with higher risk of PTE
  – Pathogenic significance remains unclear
• Further exploration of IEDs as risk factor / biomarker is warranted
• PTE is associated with higher risk of refractory epilepsy
• Further studies of PTE needed to better understand natural history
Epileptogenesis after TBI: Biomarkers and Variability

December 2, 2012

Samuel Wiebe, MD
University of Calgary
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• To explore biomarkers for post-traumatic epilepsy
  • Biochemical, genetic, imaging, clinical

• To explore the heterogeneity of risk for post-traumatic epilepsy
No Endophenotype for PTE

- If Temporal lobe epilepsy, 50% have MTS
- MRI gliotic scar and cortical hemosiderin
- Routine EEG not helpful
- Video-EEG
  - Seizures are most commonly focal (90%)
    - Temporal 54%
    - Frontal 33%
  - Selection bias

Jennett et al, Epilepsia 1975; Diaz-Arrastia et al, Epilepsia 2009
Haptoglobin as a biomarker of PTE

• Neutralizes and removes extracellular hemoglobin
• Hp increased after TBI
• Hp 1-1 more effective than Hp 2-2
• Ratio of Hp 2-2 to Hp 1-1 increased in generalized epilepsy
• Marker for development of PTE?

Anderson et al, E&B 2009
Serum Haptoglobin Phenotypes

Case-control study

Percent with phenotype

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<tr>
<th>Phenotype</th>
<th>PTS n=50</th>
<th>No PTS n=50</th>
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<tr>
<td>Hp 1-1</td>
<td>22</td>
<td>12</td>
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<tr>
<td>Hp 2-2</td>
<td>34</td>
<td>40</td>
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$p = 0.88$

Anderson et al, E&B 2009
APOE-ε4

• Produced in response to injury
• Antioxidant, anti-inflammatory, anti-excitotoxic
• ε4 allele less favourable outcome

Anderson et al, E&B 2009
APOE genotype as a marker
cohort study n=106

Diaz-Arrastia et al, Arch Neurol 2003
APOE genotype as a marker case-control study

Anderson et al, E&B 2009
MRI- endophenotypes?

- N=135, PTE 20, MRI 4-6 months
- Gliotic wall surrounding hemosidering
- Probability of PTE at 10 years

Messori et al, Epilepsia 2005
MRI endophenotypes?

DTI

P<0.001

Control
TBI no Epilepsy
TBI Epilepsy

Gupta et al, Epilepsia 2005
Maturational aspects of epilepsy mechanisms

Sanchez & Jensen, Epilepsia 2001
Effect of age on PT seizure susceptibility

Adapted form: Jyoti et al, Neurosci Lett 2009
Heterogeneous study methods

From: Lowenstein, Epilepsia 2009
Methods

• Population
  – Civilian, military, adult, paediatric, inpatient, outpatient, trauma centre, rehab centre

• Criteria
  – All TBI, CT head, GCS cut-off, specific study criteria

• Seizure diagnosis
  – Clinic, questionnaire, chart, telephone, MD, interviewer
  – Criteria: Late? Early? Epilepsy?
Implications for Clinical Practice

• New biomarkers of risk are promising, in particular MRI techniques
• No definitive genetic biomarkers yet
• Variability of methods produces heterogeneous results of risk of PTE
• Assess carefully when estimating risks for individual patients