Traumatic Brain Injury: Risk of Cognitive Impairment

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The Story of Dave Duerson

- Safety for Chicago Bears
- Three Pro Bowls
- Committed suicide Feb 17, 2011 with gunshot to chest after bankruptcy, personal problems, mental and cognitive problems
- Requested his brain be studied at Boston University
- Neuropathological examination confirmed dx of “chronic traumatic encephalopathy”
And....Junior Seau

• NEVER diagnosed with a concussion
• Played 20 years
• Committed suicide after emotional turmoil, depression, insomnia and cognitive problems
• Neuropathological examination (blinded) confirmed “chronic traumatic encephalopathy”
Spectrum of TBI

Subconcussion

Concussion (mild TBI)

Moderate TBI (GCS 9-13)

Severe TBI
GCS 3-8

Multiple hits

Chronic traumatic encephalopathy
Traumatic Brain Injury

• In the USA, about 1·6 million people sustain traumatic brain injuries every year

• Main cause of death and disability less than age 35

• 800,000 receive early outpatient care and 270,000 require hospitalization

• 52,000 deaths and 80,000 permanent severe neurological disabilities

• TBI usually the result of traffic accidents (nearly 60%), falls (20–30%), contact sports and work-related accidents (10%), or violence (10%).
TBI and Glasgow Coma Scale

Mild TBI (Concussion) = GCS of (13)14-15
Moderate TBI=GCS of 9-13
Severe TBI=GCS of  3-8
Pathophysiology of TBI

• Primary injury = acceleration/deceleration injury
  – Focal and Diffuse
  – Penetrating and non-penetrating
  – Only **PREVENTION** effective

• Secondary injury-reaction to the primary injury with increased ICP, inflammation
TBI-focal injury in fronto-temporal poles
Intraparenchymal bleeding, cerebral contusion, epidural, and subdural hematomas before and after craniotomy
Diffuse axonal injury

- Shearing injury to axons
- Acceleration/deceleration
- Corpus callosum, tegmentum of pons
Decompressive Hemicraniectomy in Diffuse TBI (DECRA Trial)

NEJM 2011:364:1493

Figure 2. Cumulative Proportions of Results on the Extended Glasgow Outcome Scale.
Concussion (mild TBI)

• 90% of TBI is “mild”
• Transient neurological dysfunction
• Does NOT require loss of consciousness
• Confusion and amnesia (AAN)...dizziness, unsteadiness, altered consciousness, disorientation, amnesia
• May take days, weeks, months to fully recover
Concussion
(American Congress of Rehabilitation Medicine)

1. Any period of loss of consciousness;

2. Any loss of memory for events immediately before or after the accident;

3. Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and

4. Focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following:

   - loss of consciousness of approximately 30 minutes or less;
   - after 30 minutes, an initial Glasgow Coma Scale (GCS) score of 13-15; and
   - posttraumatic amnesia (PTA) not greater than 24 hours.
Forces leading to concussion

- Hybrid Crash Dummies of simulated NFL concussions showed mean Linear acceleration of 98 ±28 g  

- Head Injury Telemetry System (HITS) in 88 collegiate athletes showed concussions associated with accelerations of 60-169 g  

- HITsp Forces predictive of concussion in high school players include linear acceleration of 96 g, rotational acceleration of 5,500 rad/s, and locations of front, top, and back of the head.  
Cognitive effects of impact in NCAA sports
McAllister TW, Neurology 2012;78:1777-84

- Cohorts from 3 NCAA Div I schools-high contact (football, hockey) and low contact sports
- Measured ImPACT and subset with neuropsychological testing pre- and postseason
- Post season worse performance in high contact athletes
- Poorer performance on ImPACT and other tests associated with higher impact by HITS
Post Concussion Syndrome

A. History of head trauma with loss of consciousness precedes symptom onset by maximum of 4 weeks

B. Symptoms in three or more of the following symptom categories:
   - Headache, dizziness, malaise, fatigue, noise tolerance
   - Irritability, depression, anxiety, emotional lability
   - Subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment
   - Insomnia
   - Reduced alcohol tolerance
   - Preoccupation with above symptoms and fear of brain damage with hypochondriacal concern and adoption of sick role

MRI changes after TBI

• Progressive atrophy of white and gray matter after TBI

• Diffusion tensor imaging showing loss of white matter integrity, a correlate of diffuse axonal injury
Long term volume loss after severe TBI
Sidaros et al Neuroimage 2009; 44:1-8

MRI scans at 8 weeks and 12 months

TBI patients with volume loss at 8 weeks (8.4%) with continued volume loss at 12 months (4 %)

Volume loss in brainstem, putamen, thalamus, corona radiata, corpus Callosum

Atrophy a reflection of Diffuse axonal injury

Reduction in MRI volumes 8 weeks to 12 months post TBI (red/yellow is volume loss; blue is volume gain)
Toronto TBI Study
Levine, Neurology 2008;70:771

- 69 consecutive TBI patients followed with MRI at one year
- A stepwise and dose response relationship between severity of TBI and atrophy (severe, moderate, mild, and normal)
- Frontal, temporal and cingulate regions effects most evident
Diffusion tensor imaging after TBI

DTI measures integrity of white matter tracts

“Fractional anisotropy” (FA) is a quantitative measurement of the integrity of the tracts

Decreased FA found in all cases of TBI, even in mild TBI

“White matter load” calculated and the load correlates with poor cognition on neuropsychological testing

DTI provides an objective measurement of cognitive deficits linked to TBI, even years after the injury

Kraus, Brain 2007;130:2508
Major depression after TBI

JAMA 2010;303:1938
Repetitive concussion

• Sports injuries; blast injury in military
  – NFL players-Dave Duerson, Junior Seau

• Concern this may lead to “chronic traumatic encephalopathy and cognitive decline

• Individual susceptibilities
  – Genetic
  – Alcohol use
  – Educational level; prior level of intellectual function
Chronic Traumatic Encephalopathy

Goldstein et al Sci Trans Med 2012

45 yo military veteran with blast injury 2 yrs previous
34 yo military veteran with 2 blast injuries but no concussion
18 yo football player with repetitive concussions
21 yo football player with repetitive sub-concussive injuries
Chronic traumatic encephalopathy

- Same pathophysiological process of phosphorylated tau deposits in IED blast injuries to military and civilian football players

- Irritability, anxiety, depression, cognitive decline, suicide

- Many of these injuries not recognized to be severe or even “concussions” at time

- NFL lawsuits

- NFL just donated 30 million to NIH Foundation
Chronic traumatic encephalopathy

- Blast injury model in mice
- Models the chronic traumatic encephalopathy seen in military and civilian head injury
- We can now test therapies to prevent the pathophysiological process
Genetic factors predisposing to cognitive decline after concussion

- apoE alleles-APOE4
  - Associated with risk of Alzheimer’s disease
  - APOE4 allele may be associated with long term poor outcome (6 months) after TBI (J Neurotrauma 2009;25:279)
  - However other studies have shown no association (Chamelian, Brain 2004;127:2621)
  - APOE4 acts synergistically with TBI to increase risk of Alzheimer’s disease R. Mayeux, Neurology 1995; 45, 555–557
Should we genotype all high school and college high contact sport athletes?

- APOE 4 homozygosity in 2% and heterozygosity on 20% of population
- 1.1 million high school football players in U.S.
- Concerns about privacy and insurability
- Genetic Information NonDisclosure Act (GINA)
TBI and Alzheimer’s Disease


OR

• TBI may just reduce “cognitive reserve” and hasten the appearance of dementia  Morreti L, Lancet Neurol 2012;11:1103
Brain injury is brain injury is brain injury

• Stroke and TBI share many common pathophysiological processes

• Secondary injury involves inflammation in both

• Drugs that work in stroke tend to work in TBI (progesterone, minocycline, etc)
New treatments for TBI

• Acute phase
  – Progesterone (NIH funded trial)
  – Stem cells-autologous and allogeneic

• Subacute phase
  – Amantadine in moderate/severe

• Chronic phase ?
Stem cells in TBI

Walker, P et al  Exp Neurology 2010;225:341
TBI Summary

1. Mild TBI is common in high school, college, and professional athletes; prevention most important intervention

2. Repeated mild TBI (concussion) and “subconcussion” may lead to cognitive decline and “chronic traumatic encephalopathy” in a subset of patients

3. MRI imaging-volumetric analysis and DTI -may serve as an “imaging” or biomarker of cognitive decline

4. Genetic factors (i.e. APOE4) and other environmental factors may determine risk