Battlefield to Ball Field: The Science, Myth and Reality of Concussion

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  – NIH
  – NIDRR

• The views expressed in this presentation are solely those of Dr. Cifu
Goals

• Paint a picture of the landscape of mild TBI in sports, civilian and military sectors.

• Highlight the recent concern over the long-term effects of mild TBI.

• Summarize the available science in acute mild TBI and potential neurodegeneration.

• Update the current research activities in mild TBI
Myths of mild TBI

• There is scientific evidence that single concussions are associated with long-term risks.
• One week of rest after a concussion is usually sufficient to allow for return to sports.
• Newer neuroimaging techniques allow us to diagnose concussion accurately.
• There are emerging biomarkers to detect concussion.
• There are no evidence based treatments for symptoms of concussion.
• Most concussions from war are blast related and have poor outcomes.
Concussions

- >3.8 million sports and recreational injury concussions annually [Langlois CDC 2006]

- >1.7 ED admissions for concussion annually [Langlois CDC 2006]

- 100,000-250,000 concussion from recent Gulf Wars [Cifu JRRD 2014]
Definitions: Concussion

- **Concussion** (= mild TBI) is a complex pathophysiologic process induced by traumatic forces secondary to direct or indirect impulsive forces to the head that disrupts the function of the brain.

- Concussion is defined as an alteration or loss of consciousness for up to 30 minutes with associated loss of memory surrounding the event (post-traumatic amnesia) for up to 24 hours.

- Transient (<24 hours) neurologic sequelae may also be present, including numbness, dizziness, cognitive deficits, discoordination, and alterations in special senses.

- This disturbance of brain function is typically associated with normal structural neuroimaging findings.
Definitions: Potentially Concussive Event

• Increasing “awareness” of potentially concussive events (PCE).

• A PCE is defined as an impulsive force to the head of sufficient intensity that results in acute or chronic symptoms in some individuals, but remain asymptomatic (“subclinical”) in others - no demonstrable neurologic or symptomatic effect.

• Concern about the long-term effects of this potential cumulative trauma disorder.
Injury caused by rotation not direct skull trauma

mTBI = Concussion

Concussion = mTBI

Helmets prevent skull fractures not concussions
Diffuse (Traumatic) Axonal Injury

- Rotational injury to the head results in stretch injury to axons and vascular structures resulting in changes to the cytoskeleton (compaction of neurofilaments, loss of microtubules) and unregulated flux in ion concentrations.
- Injury most significant along midline structures (corpus callosum, brainstem) and at cortex-white matter junction.
Diffuse (Traumatic) Axonal Injury

- Damaged white matter shows axonal swellings that most commonly in the parasagittal parts of the brain, the corpus callosum, fornix, internal capsule, and the brain stem.
- Axonal swellings can be detected with H&E and silver stains 15 hours after the injury.
- Immunostains with antibodies to Beta Amyloid Precursor Protein (BAPP) can detect the axonal lesions in 2-3 hours after the injury. BAPP flows down the axon and accumulates at points of axonal constriction or transection.
- Axonal swellings may persist for years. Distal to the swellings, axons and myelin degenerate and gliosis develops over time. Severe DAI may cause decrease of white matter volume, atrophy of the corpus callosum, and dilatation of the lateral ventricles.
Definitions:
Post-Concussive Symptoms

• Persistent physical, cognitive, emotional, and/or sleep-related symptoms occur in 50+% of concussions, but usually resolve in 1-4 weeks.

• Symptoms presenting in the first 1-2 weeks after a concussion are commonly ascribed to the concussion.

• Post-Concussive Syndrome
  – symptoms continuing for 3+ months
  – seen in 15-30% of concussions
  – continue for >1 year in 5%.
PCS Symptoms

- Headache 30-90%
- Dizziness 50%
- Psychological (irritability, anxiety, depression) 50%
- Cognitive (executive function, STM) 30-50%
- Insomnia 50%
- Photophobia 10%
- Anosmia 5%
- Blurred/Double Vision 15%
PCS Symptom Etiology

• Acutely
  – Axonopathy (3-8 weeks)
  – Alterations in glucose metabolism
  – Acute musculoskeletal/soft-tissue pain
  – Psychological
  – Iatrogenic

• Chronic [???]
  – Permanent damage to axons
  – Psychological
  – Iatrogenic

http://www.healthquality.va.gov/guidelines/Rehab/mtbi/
Sports Concussions

- Sports Concussions
- 5-9% of all sports injuries
- Highest incidence in football, wrestling, girl/boy soccer, girl’s basketball
- Higher incidence in practice than games
- Higher incidence in women vs men (same sport)
- 80-90% symptom resolution by 1 week, but unclear what this means
- History of concussion associated with 2-6x higher incidence repeat
- Headache most common symptom, followed by dizziness.
- Dizziness increases risk of slower recovery
Sports Concussions

• Return to school and play guidelines are based on “consensus.”

• Symptom management is main management tool.

• Return to school when symptoms managed. Unclear role for focal or comprehensive NP testing.

• Return to play when symptom free at rest and during activity/scrimmage.

• Symptom resolution and return to normal of brain function do not appear to be simultaneous.
Combat Concussions

- 7-12% of OEF-OIF-OND Veterans who received VA medical care have confirmed TBI
  - ~75,000 total (>800,000 screened) in VA
    - 95% mild
    - <5% moderate-severe (2,500-3,000)
  - >50% combat concussions due to MVC
  - 73% of Veterans with symptomatic mild TBI also have mental health diagnosis, most commonly Post Traumatic Stress Disorder (PTSD)
    - >90% also have either PTSD or chronic pain disorder
**Mandatory TBI Screening Results**

14 April 2007 – Present

- **Total OEF/OIF Veterans Screened**: >800,000
- **Veterans with Self-Reported Prior TBI**: ~200,000
- **Veterans Requiring Further Evaluation**: ~94,900
- **Veterans Consenting to Further Evaluation**: ~14,000
- **Veterans Completed Evaluation**: >150,000

**TBI Confirmed**
- 7.9% of total screened or 39.5% of all + screens

**TBI Ruled Out**
- ~90% have secondary psych dx; ~75% w/ PTSD

>95% of TBI’s are mild in severity

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Taylor: Med Care 2012;50:342
Carlson: J Trauma Stress 2010;23:17
Figure 1

Three Year Incidence of TBI, PTSD and/or Pain Diagnoses in OEF-OIF Veterans (2009-2011)
### Gulf Wars Injuries: DoD + VA

- More than 2.5 million Americans have been deployed, typically serving multiple tours.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputations</td>
<td>&gt; 2,500</td>
</tr>
<tr>
<td>Burns</td>
<td>&gt; 600</td>
</tr>
<tr>
<td>TBI</td>
<td>&gt; 200,000</td>
</tr>
<tr>
<td>SCI</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>PTSD</td>
<td>&gt; 400,000</td>
</tr>
<tr>
<td>MSK Pain</td>
<td>&gt; 400,000</td>
</tr>
</tbody>
</table>

Knee > Back > Neck > Headache
One Explosion/Blast has Multiple Mechanisms of Injury

Wall of Air (Primary)

Blast Wind (Primary)

Flying Debris (Secondary)

Displacement (Tertiary)

Collapse Building (Quaternary)
Blast mTBI

- Limited (no) controlled studies. **No** pure blast injuries.

- MacDonald demonstrated DAI of cingulum bundles, orbitofrontal white matter and middle cerebellar peduncle (NEJM 2011;364:2091-2100)
VHA Polytrauma/TBI System of Care FY 2013

Legend
- Polytrauma Rehabilitation Center
- Polytrauma Network Site
- Polytrauma Support Clinic Team
- Polytrauma Point Of Contact

Alaska
Philippines
Hawaii
Puerto Rico
Post-Deployment Syndrome Management

- **Education**
  - Diagnosis – explain multiple contributors
  - Prognosis – optimism, self-actualization
  - Health Management - Fitness, Sleep, Diet, Mind/Body

- **Interventions**
  - Sleep – sleep hygiene, medications
  - Pain – pain management, non-narcotic medications (short term)
  - Behavior – counseling, mood stabilizers (at full dosing)
  - Cognition – adaptive strategies, assistive technology
  - Fatigue – sleep, fitness, diet, counseling

- **Goals**
  - Normalization
  - Deinstitutionalization
  - Return to productivity and activity
  - Reintegrate into social roles and activities

http://www.healthquality.va.gov/guidelines/Rehab/mtbi/
Combat vs. Sports concussions

**Combat**
- Etiology: Blast + Rotation
- Severity: Mild
- Number: 1-150 in 1-10 years
- Treatment: Variable
- Secondary injury: Extensive, polytrauma, psychological

**Sports**
- Etiology: Focal + Rotation
- Severity: Mild to Moderate
- Number: 100-8,000 in 30 years (Pee Wee to Pros)
- Treatment: Variable
- Secondary injury: Limited musculoskeletal

Are long term consequences similar?
Non-Sport Civilian Concussions

- Most common cause is MVC.
  - Airbags have decreased TBI fatality and increased mTBI.
  - Whiplash (neck) injury almost always accompanies.
  - Concussions are commonly overlooked.

- Symptom management is main management tool.

- Medicolegal issues complicate management and recovery.

- Elements of sport and combat mTBIs in MVC injury.
Neuroimaging

While we have amazing technology, images and advancing science, it’s unclear what to actually do with brain imaging for acute clinical care, long-term management or prediction or research.
DTI

- DTI works by measuring the diffusion of water through tissue. Measurements are isolated to identify the preferred direction of flow, which allows for the isolation of neural tracts from the brain’s white matter. DTI is the most sensitive MR approach currently available and can be used to identify tract-specific lesions caused by TBI.

- Highly sensitive but finding may be non-specific
**SWI**

- Susceptibility weighted imaging (SWI) image is possible through the use of algorithms that differentiate the densities of adjacent tissues. While signal density forms the basis of all MR scans, the SWI scan is 3-to-6 times more sensitive as it accounts for the susceptibility of all brain elements, including hemorrhages – hence the name susceptibility-weighted image.

- SWI was formerly known as blood-oxygen level dependent (BOLD) imaging. It is very sensitive to bleeding, and can be useful in the petechial hemorrhage that occurs in the gray-white zone with DAI.
Diffusion-tensor tractography uses the data collected from diffusion weighted imaging. DWI measures the diffusion behavior of water molecules and is used to produce DTI.

- Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) are measures of DWI.
• **Positron emission tomography (PET)** is a nuclear medicine, functional imaging technique that produces a three-dimensional image of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule.

• PET-FDG uses a tracer that is an analogue of glucose and the concentrations of tracer imaged will indicate tissue metabolic activity by virtue of the regional glucose uptake.

• PET-TAU uses fluorine-tagged ligands to detect tau protein.
Biomarkers for mTBI

• Extensive research efforts to identify CSF, blood, urine and/or salivary biomarkers of TBI.
• Acute injury markers in CSF of moderate-severe TBI defined in rodents and have fair sensitivity but poor specificity in humans.
• No clear acute or chronic biomarkers for mild TBI
# Potential Fluid Biomarkers of mTBI

<table>
<thead>
<tr>
<th>Marker</th>
<th>Process or structure affected</th>
<th>Research findings in mild TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal fluid: serum albumin ratio</td>
<td>Blood-brain barrier</td>
<td>Detection method not sensitive enough to changes in concentration(^{33,14})</td>
</tr>
<tr>
<td>Interleukins and other acute-phase inflammatory response proteins</td>
<td>Neuroinflammation</td>
<td>NA</td>
</tr>
<tr>
<td>Total tau protein</td>
<td>Axon</td>
<td>Levels peak 4–10 days after injury(^{34,71})</td>
</tr>
<tr>
<td>Myelin basic protein</td>
<td>Axon</td>
<td>Elevated levels in hypoxic brain injury(^{101,102}); studies in mild TBI are lacking</td>
</tr>
<tr>
<td>Neurofilament light polypeptide</td>
<td>Axon</td>
<td>NA</td>
</tr>
<tr>
<td>Neurofilament heavy polypeptide</td>
<td>Axon</td>
<td>Detection methods not sensitive in mild TBI(^{79})</td>
</tr>
<tr>
<td>γ-Enolase</td>
<td>Neuron</td>
<td>Serum levels very sensitive to lysis of red blood cells in blood-contaminated cerebrospinal fluid(^{42})</td>
</tr>
<tr>
<td>S100-B</td>
<td>Astroglial cells</td>
<td>Levels are elevated, but a less sensitive marker than tau protein and neurofilaments(^{73})</td>
</tr>
<tr>
<td>Glial fibrillary acidic protein</td>
<td>Astroglial cells</td>
<td>Serum levels correlate with changes on brain imaging(^{115}); extracerebral protein has not been detected(^{15})</td>
</tr>
<tr>
<td>Secreted APP-α and APP-β</td>
<td>Axon</td>
<td>NA</td>
</tr>
<tr>
<td>Amyloid-β(^{40}) and amyloid-β(^{42})</td>
<td>Plaque pathology</td>
<td>No change in levels(^{57,74})</td>
</tr>
<tr>
<td>Spectrin breakdown products</td>
<td>Neuron</td>
<td>NA</td>
</tr>
<tr>
<td>Ubiquitin carboxyl-terminal hydrolase isoenzyme L1</td>
<td>Neuron</td>
<td>One pilot study showed promising results(^{123})</td>
</tr>
<tr>
<td>Peripheral blood mononuclear small noncoding RNA molecules</td>
<td>Unknown</td>
<td>One pilot study suggests altered expression of three RNA molecules in mild-TBI-exposed military personnel(^{126})</td>
</tr>
</tbody>
</table>

Abbreviations: APP, amyloid precursor protein; NA, not available; TBI, traumatic brain injury.
Q: Do TBI’s predispose for late life degeneration?

A: Yes
Chronic Traumatic Encephalopathy

NFL players sustain 3,000-8,000 concussions during a lifetime of sports
Iraq War combatants (U.S.) with mTBI report 1-151 mTBIs (~4 average).

NFL players sustain 3,000-8,000 concussions during a lifetime of sports.

Your speaker has sustained 5-6 concussions in his timid, little life.
Traumatic Brain Injury (TBI)

- Diffuse axonal injury, mechanical tissue damage, ischemia, synaptic loss, neuronal dysfunction or demise
  - Impaired axonal transport, neuronal circuit disruption

Mild TBI
- Contusion, mild edema, uncertain short-term pathology
  - Neurofibrillary tangles (tauopathy)
  - Dementia pugilistica; chronic traumatic encephalopathy; pugilistic parkinsonism
  - Variable chronic cognitive or neuropsychiatric impairment; frequently associated with post-traumatic stress disorder

Mild Repetitive TBI
- Axonal and cytoskeletal alterations, accumulation of abnormal protein aggregates
  - Tendency toward neuropathology modified by APOE e4
  - Dementia pugilistica; chronic traumatic encephalopathy; pugilistic parkinsonism

Severe TBI
- Chronically impaired neuronal homeostasis, accumulation of abnormal protein aggregates
  - Aβ and tau pathology
    - Alzheimer’s disease
  - Reestablishment of neuronal homeostasis, clearance of abnormal protein aggregates
  - Total or partial functional recovery, often with variable chronic cognitive or neuropsychiatric impairment
Chronic Traumatic Encephalopathy

- CTE (Punch Drunk, Dementia Pugilistica) begins insidiously, usually many years (5-20) after the patients have stopped playing sports, with inattention, mood and behavior disturbances, confusion, and memory loss, and progresses over many years (5+) to a stage of full blown dementia and Parkinsonism.

- The brain, in CTE, shows atrophy, dilatation of the lateral and third ventricles, and thinning of the corpus callosum.

- Microscopic examination reveals neuronal loss and tau deposition in neurons (neurofibrillary tangles-NFTs) and in astrocytes. This pathology involves the cerebral cortex (perivascular areas, deep), white matter, deep nuclei, and the brainstem.

- Beta amyloid deposition in the form of diffuse and less frequently neuritic plaques is seen inconstantly.
TBI and Degenerative Disorders

• Increasing evidence supports that
  – Even a single moderate to severe traumatic brain injury (TBI) is a risk factor for the development of Alzheimer’s disease (AD) in later life
  – Multiple mild TBIs (concussions) may lead to chronic traumatic encephalopathy (CTE)
  – A few pathological studies suggest that a single TBI may be associated with increased tau accumulation
  – However, definitive longitudinal studies are lacking.

• AD is characterized neuropathologically by beta-amyloid neuritic plaques and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein.

• CTE is characterized by accumulation of NFTs structurally indistinguishable from those of AD, and few, if any, neuritic b-amyloid plaques.
Chronic Traumatic Encephalopathy
Chronic Effects of Neurotrauma Consortium

• Departments of Defense and Veterans Affairs-funded nationwide research consortium to study the short- and long-term effects of repeated concussions in combat injured servicemembers and Veterans.

• Five year, $62.2 million award begun October 2013.

• Partner with NIH, NINDS, NCAA and NFL research groups to jointly study civilian, sports and combat concussions.

CENC.RTI.ORG
Chronic Effects of Neurotrauma Consortium

• VCU Department of PM&R (Cifu, PI) is coordinating this nationwide consortium
  – 8 Universities: VCU, USF, USUHS, BCM, UT-San Antonio, UC-SF, UW, UH
  – 3 Military Sites: Ft. Belvoir, BAMC/SAMMC, WRAMC
  – 3 Institutes: Roskamp, Barrows, RTI
  – 6 VAMC: Richmond, Tampa, Houston, San Antonio, Mountain Home, San Francisco

• 6 funded research cores
  – Administrative/Leadership – VCU
  – Database and Biostatistical - RTI
  – Biomarker – USUHS
  – NeuroPathology - USUH
  – Imaging - BCM
Chronic Effects of Neurotrauma Consortium

- **Longitudinal Study (VCU/Richmond VAMC)** – 1,000 Veterans/SMs with combat mTBI (100 controls) seen 1-15 years post-injury. Comprehensive evaluation every 2 years and phone f/u in between.
- **Basic Science Tauopathy (Barrows/Roskamp)** – Tau-mouse study of repeated mTBI in young and aged mice.
- **Epidemiologic (UCSF)** – Epidemiologic study using existing VA, DoD and CMS databases to examine TBI, dementia, PD, psychological diagnoses.
- **Otolith Rehabilitation (Mountain Home VAMC)** – Prospective study of 60 mTBI Veterans with dizziness utilizing specific otolith-based intervention.
- **ADAPT (UW)** – Longitudinal f/u (1-3 years) study of 100 SMs with Gulf War mTBI imaged and assessed in theatre
- **DTI Phantom (BCM)** – Identification and development of standardized DTI phantom for mTBI
Chronic Effects of Neurotrauma Consortium

• Currently considering 28 study proposals for funding ($22 million available).
  – CAM intervention
  – Tau Pet imaging
  – Longitudinal
  – Biomarker
  – Neuroendocrine
  – PCS intervention (exercise, medication)

• Part of the newly NIH-funded $18.8 million Transforming Research and Clinical Knowledge in TBI (TRACK-TBI II) study.
  – 20 site nationwide consortium to study civilian TBI longitudinally.

• Part of multi-site NINDS C-LEARN proposal ($13 million) submission.
  – Nationwide consortium to study NFL/Sports concussion longitudinally.
TBI Outcomes Research: Searching for the Answer

• Large, longitudinal studies using standardized metrics

• Risk factors
  – Acute: Stress, Substance Use, Repeated injury, Severity of Injury, Timing of Injury Genetics, Environmental
  – Chronic: Stress, Mental Illness (Depression), Cardiovascular, Smoking, Substance Use, Cognitive Disuse, Steroid Usage

• Interventions
  – Education
  – Return to Productive Activity
  – Cognitive Stimulation
  – Social Integration
  – Wellness and Health Maintenance
  – Prevention
Myths of mild TBI: Revisited

• There is scientific evidence that single concussions are associated with long-term risks. *Single moderate-severe TBIs*

• One week of rest after a concussion is usually sufficient to allow for return to sports. *Most symptoms are gone but is brain recovered?*

• Newer neuroimaging techniques allow us to diagnose concussion accurately. *No gold standard.*

• There are emerging biomarkers to detect concussion. *None.*

• There are no evidence based treatments for symptoms of concussion. *Extensive management protocols available.*

• Most concussions from war are blast related and have poor outcomes. *Unclear contribution of blast. Most are MVCs.*
Thank You