Pathophysiology of Concussion & Advances in Neuroimaging: An Update for Clinicians

Michael Gay, MS, ATC
Assistant Athletic Trainer
Pennsylvania State University
VIDEO:

Concussion Up-Date

Objectives:

- Review the events surrounding acute mild traumatic brain injury.
- Describe the pathophysiology and physical effects of concussion.
- Review current diagnostic approaches to mild traumatic brain injury.
- Summaries of treatment strategies in currently reviewed in the TBI literature.
Concussion: Incidence

- **Sports:**
  - Cause about 18% of all concussions

- **High school:**
  - 0.24 concussions/1000 athlete exposures
    - Football 0.60/1000
    - Girl’s soccer 0.35/1000

- **College:**
  - 0.40-0.60 concussions/1000 athlete exposures
    - Football 2.7/1000
    - Ice hockey 1.4/1000
    - Men’s/Women’s soccer 1.1 – 2.1/1000

# - Copeland, J.: *New Data Suggest Shift in College Football Concussion Rate;* www.ncaa.org published report
Recognition and Management
“If an athlete exhibits any signs, symptoms, or behaviors that make you suspicious that he or she may have had a concussion, that athlete must be removed from all physical activity, including sports and recreation. Continuing to participate in physical activity after a concussion can lead to worsening concussion symptoms, increased risk for further injury, and even death.”

Source: http://www.nfhs.org/content.aspx?id=3325
State Level Concussion Legislation:

PA – SB/HB 200 *The Safety in Youth Sports Act*

- Establishes standards for managing concussions at the high school and middle school level, including club sports
- Concussion education form completed yearly by student and parent.
- Athlete must be removed from game by medical staff, coach, or official if displaying concussive symptoms. Athlete “shall not return to participation until the student is evaluated and cleared for return to participation in writing by a licensed or certified health care practitioner whose scope of practice includes the management and evaluation of concussions.”
- Coaches required to complete concussion education through the CDC, NFHS, or Dept. of Health annually.
Institutes must have a concussion management plan:

- This plan should outline the roles of athletic healthcare staff.
- Institutions should ensure that coaches have acknowledged that they understand the concussion management plan, their role within the plan and that they received education about concussions.
- Athletics healthcare providers should practice within the standards as established for their professional practice.

Source: 2010-11 NCAA Sports Medicine Handbook; Concussion or Mild Traumatic Brain Injury (mtbi) in the Athlete, Section 2i, pp. 52-56
NCAA Concussion Management Plan

- **NCAA**

  - **Baseline Assessment:**
    - At a minimum, the baseline assessment should consist of the use of a symptoms checklist and standardized cognitive and balance assessments.
      - SAC; SCAT; SCAT II; Balance Error Scoring System (BESS)
    - *Strongly recommends* the adoption of a neuropsychological testing battery either pencil and paper or computerized forms.

*Source: 2010-11 NCAA Sports Medicine Handbook; Concussion or Mild Traumatic Brain Injury (mtbi) in the Athlete, Section 2i, pp. 52-56*
NCAA Concussion Management Plan

NCAA

Individual Components

- Symptomatic athlete should be removed from activity and evaluated by medical staff.
- Concussed athlete cannot return to play that day.
- Discharge instructions and serial monitoring.
- Evaluated by team physician, return-to-play process started once asymptomatic
- Team physician or designee makes final RTP decision
- Documentation of overall injury, evaluation, management, and clearance

Source: 2010-11 NCAA Sports Medicine Handbook; Concussion or Mild Traumatic Brain Injury (mTBI) in the Athlete, Section 2i, pp. 52-56
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- Definition of Mild Traumatic Brain Injury
- Mechanisms / Forces
- Physiology of Injury Phases
  - Acute Injury
  - Sub-acute Phases
- Neuroimaging Techniques & Research
- Treatment Approaches to mTBI
“Sports concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces”.

- Usually results in rapid onset and short-lived spontaneously resolving impairment
- Symptoms generally reflect a functional and structural disturbance in homeostasis.

• Classification systems have been abandoned

Compressive forces, tensile forces, rotational forces induce injury at the cellular level. Leads to biochemical changes related to disruption of homeostasis:

- Ultra structural changes to White Matter, Cellular Membrane Disturbance, Metabolic Demand Changes etc.
- Environment leaves the brain susceptible to second impact syndrome

**Source:** Dr. Jay Rosenberg of Kaiser Permanente Medical Care Neurology; American Academy of Neurology, The Human Body
Mechanical Forces leading to primary diffuse axonal injury (DAI):

- Acceleration / Deceleration of the brain inside the skull (Coup / Countercoup phenomena)
- Shearing, tensile and compressive stresses on neural tissues.
  - Most damaging may be shearing type forces.
  - Tend to focalize along brain stem due to structural anatomy of the brain and concentration of mechanical forces along a fixed point. (Tethered)
- Stretch forces can induce up-regulation of genetic transcription factors for both apoptosis and neurotrophic growth factors.
Acute insult to neural tissue:
- Primary Damage
  - Responsible for focal lesions, vascular compromise (intracranial bleeds), diffuse axonal injury, disruption of cellular membranes

Secondary Sequelae to Injury
- Ischemic Environment
  - Change in local vascular/↑ATP demand may be lasting effect.
- Metabolic Shift
  - Energy consumption (bioenergetics)
  - Substrate Shift
- Neuroinflammatory response
  - Healing process→Neuron (Soma vs. Axon)
Ischemic/Metabolic Event

Circulatory changes
- Vasoconstriction as a result of the localized release of vasoconstrictive cytokines.

Metabolic changes within the neuron
- Rapid release of neurotransmitters and other macromolecules into the extracellular space.
- Result in an increased metabolic demand (ATP dependant processes of returning to cellular homeostasis).
- Creation of metabolic vulnerability (< 5 days animal model) where the brain is susceptible to further injury (Second Impact Syndrome).

Shift in substrate utilization
- Use of lactate/pyruvate as primary energy sources of ATP.
- Decreased use of glucose in the neuron for ATP.
  - Mitochondrial function in the Astrocytes, Disrupted function in the Neuron.
Sub-Acute Injury

- Neuro-inflammatory response:
  - Reactive Oxygen Species (ROS)
    - Produced from perioxidized membrane phospholipids.
  - Cellular healing process:
    - Key Players: Macrogial cells (Astrocyte), Microglial Cells (Macrophages).
    - Glial cell production of proinflammatory cytokines (TNF-α) creating chemotactic gradient resulting in increased inflammatory response → Leukocyte infiltration.
    - T-Cell Activation: Leads to release of neurotrophic growth factors (BDNGF, NT-3, NT-4).
Diagnostic Approach to mTBI

- Neuropsychological Evaluation
- Neuroimaging Techniques
- EEG Analysis
Neuropsychological Evaluation

- Functional testing used to determine the extent of the functional limitations in cognition.

- Used to examine current level of Executive Functioning across different domains.
  - Verbal memory, visual memory, speed of cognition, reaction time, cognitive fluency etc.

- Administration of a fixed battery of tests allows for comparison of the results to normative data sets.
  - Needs a baseline to become more accurate to the individuals performance.
Diagnostic Approach

- **Positives**
  - Allows clinicians the ability to assess the current neurological functioning of the patient being tested.
  
  With computer based testing the test can be completed in a short amount of time with little supervision.
  
  Allows clinician to individualize the rate of recovery for cognitive domains being assessed when coupled with a comprehensive clinical exam and symptoms resolution.
  
  Interpretation requires specialized neuropsychologists as trained clinicians for proper interpretation of the results.
Additional Considerations

Influential factors

- Age / Group related neural maturation
  - Frontal lobe development lasts into the third decade of life.
- Practice Effects
- Cognitive Reserve (Intelligence Testing)
- Learning Disability
- Fatigue, Diet (Vegetarians)
- Motivation (i.e. Depressive Disorder)
- Patient History
  - Severity and number of previous concussions
Neuroimaging techniques

MRI, CT Scans:
- Traditional limitations
  - Typically negative in mild traumatic cases

Functional MRI (fMRI)
- Advances in scanning techniques and quality of measurement.
- DTI / DSI, Spectroscopy, BOLD signal detection, Connectivity etc.
Diffuse Tensor Imaging

- Evaluation of the general function of white matter tracts
  - Measures the changes of the diffusion of water (Anisotropy) along axons, thus identifying axonal compromise / injury.
  - Fluctuations in values can be considered areas of inflammation or damage.
  - Assumes homogeneity within the voxel being measured.

Diffuse Sensor Imaging

- Increased sensitivity by considering bi-directional flow (heterogeneity of tracts).
### Magnetic Spectroscopy

- Detection of the common metabolites within White Matter / Gray Matter
  - Lactate (energy substrate)
  - Creatine (energy molecule)
  - N-Acetylaspartate (myelin sheath)
  - Choline (membrane compound)

- Has promise for examining metabolic recovery. Need for a standardized voxel based approach. Metabolic ratios can remain altered for up to 30 days post injury independent of self-reported symptom status.

*(Vagnozzi et. al. 2010)*
B.O.L.D. signal

Blood Oxygen Level Dependence scanning
- Signal identifies the differences between oxygen saturation in the blood (Oxygenated vs. Deoxygenated blood).
- Identifies metabolically active groups of neurons.

Current application
- Neuropsychological research applied to NP testing batteries.
- BOLD signal activation has been used to confirm altered brain activation in subjects recovering from TBI when performing different NP Tasks. (*Slobounov et. al. 2010*)
- ‘Resting State’ or ‘Small World Network’ function has been used to confirm differences between pathologic/non-pathologic states. (*Schizophrenics*) (*Mannell et. al. 2010*)
- Functional Connectivity between regions in the brain.
Diffuse Tensor Imaging
- Anisotropic values altered
  - 30 days, 3 months, 6 months (Cubon 2011, Niogi 2008, Smits 2010, Kumar 2009, Wozniak 2007)

Spectroscopy
- Whole Brain metabolite ratio imbalance 30 days
  \( (Vagnozzi, 2008) \), 120 days → Grey Matter vs. White Matter
  \( (Yeo, 2011) \)

BOLD Signal
- Functional Connectivity Alterations (Resting State vs. Default Mode Network) \( (Slobounov 2010) \)
Electroencephalogram (EEG)

- **EEG Evaluation**
  - Measures electrical activity in the brain at varying frequency bands:
    - Delta (< 4 Hz), Theta (4.5 – 8 Hz), Alpha (8-12 Hz), Beta (12.5 – 36), Gamma (> 36 Hz)
  - As well as at rest or in sleep studies, EEG is used in combination with other tests to measure electrical activity in the brain during cognition.
  - Relevant measures:
    - Coherence representing changes in connectivity / Small World Network
    - Absolute Power within frequency bands
    - Evoked Potentials or Event Related Potentials (ERPs)
Penn State – Concussion Laboratory
- 32 Lead – EEG analysis
- Virtual Reality-NP Testing
- Virtual Reality-Visual Kinesthetic Balance
  - COP Measurements (Force Platform)
  - http://pennstatetbi.weebly.com/
Digital Eye Tracking Devices

- Saccadic / Anti-Saccadic Movement, Gaze error variability, smooth pursuit (*Maruta J et. al. 2010*)
- Eye Tracking research was used to develop King-Devick sideline assessment test.
Treatment

Neuroinflammatory Responses

Metabolic Responses

Prevention
Hypothermia (TBI research)
- Concept is that the decreased temperature decreases ATP demand in metabolically strained environment.

Research is varied:
- **Factors:** Age, Sex, Timing, Injury Severity
- Reproducible animal models have demonstrated the effects of post-traumatic hypothermia (30-33°C) have:
  - Reduced contusion volume, Increased neuronal survival
  - Reduced sensorimotor / cognitive deficits
  - Reduced presence of beta-precursor proteins (sign of injury in white matter tracts, Diffuse Axonal Injury)
  - Reduced presence of pro-inflammatory cytokines: IL-1β, TNF-α
  - Reduced apoptic cell death (Caspase 3 inhibition)
Treatment: Metabolic

- Creatine
  - Cerebral Ischemia / Stroke
    - Neuroprotective in hypoxic-ischemic injury
    - Reduced Stroke Volume (effected area)
    - Possible effect on vasodilatory response in the injured area
    - Preservation of bioenergetic cellular status & inhibition of activation of caspase cell-death pathways (apoptosis). *(Zhu et. al. 2004)*
  - Traumatic Brain Injury
    - Cr administration resulted in significantly better outcomes:
      - Cognition, personality / behavioral, self-care and communications
Delivery of Oxygen \((\text{O}_2)\)

- Perfusion therapy
  - Perfluorocarbon emulsion therapy (Oxycyte emulsion)
  - Demonstrated improved restoration of cognitive function after lateral fluid percussion injury in rats. \((\text{Zhuo et. al. } 2008)\)

Hyperbaric Chambers

- Treatment of 100\% \text{O}_2 with greater atmospheric pressures
- Observed in TBI research
- Demonstrated decreased neuronal cell death
- Case report on airmen with PCS after roadside IED. Resolution of sleep disturbance, headaches, cognitive difficulties, memory difficulties \((\text{Wright et. al. } 2009)\)
Vitamin E

- Vitale for the structural survival of lipid membranes
  - Neuron & Mitochondrial
  - Capable of breaking the lipid peroxidation reaction chain.
    (Process mediated by ROS)

- Preserves energy homeostasis through preservation of anti-oxidant actions.

- Maintains synaptic health through preservation of the production, regulation of BDNF.
Omega-3 (DHA)

- Anti-oxidant actions similar to Vitamin E
- Indirect actions on energy metabolism preservation cytokines. AMPK & uMtCK (Wu et. al. 2010)
- Microglial cell: Down regulation of pro-inflammatory cytokines (Zhang et. al., 2010)
- COX inhibitor, Reducing pro-inflammatory cytokines (IL-6, IL-1, TNF-α) and eicosanoids. (Bailes, 2010)
Treatment: Neuroinflammatory

- **Exogenous IGF-1 Administration:**
  - IGF-1 administration lead to decrease in apoptosis
  - Mechanism: Increased expression of endoplasmic reticulum anti-apoptotic cellular proteins and preservation of protein folding function of the ER.
  - Result: Increased number of neurons which were able to survive mTBI insult. (Animal Model)

*Ultimately preserved homeostatic cellular function via properly functioning ER*
Treatment: Exercise

What are the effects of Exercise?


Does Physiology Play a Role?

- Prescription: When? How much?
- What’s the difference? Mitochondrial Biosynthesis
Future Challenges

- Clinical Testing vs. Neuroimaging
  - Can we close the gap? How do we use neuroimaging?
  - Use research to drive clinical testing (For example: King Devick Exam)

- Rethink “Return to Play”
  - Are we conservative enough? 30 Days?
  - Do we need more rigorous clinical examination?
  - Concept of Graded Clinical Exams?

- Treatment
  - Metabolic / Anti-inflammatory treatment designs.
  - Exercise as a treatment.
  - Physiology the key? Athletes vs. Sedentary brain.
THANK-YOU

Go State...