# Concussion: Approaching a Changing Landscape

An Evidence/Informed-Based, Interdisciplinary Approach

Benjamin R. Siebert, MD, FAAPMR

excellence in brain, spine and pain care

neurosciencegroup







### Disclosures



Medical Advisory Board, Prevacus, Inc. -stock option



#### Objectives

- I. Review and improve understanding of pathophysiology of Traumatic Brain Injury
  - I. Understanding TBI
  - II. Epidemiology
- II. Apply changes to current practice models to improve outcomes and enhance recovery in concussion





# Understanding...













#### **Traumatic Brain Injury**

#### Center for Disease Control (CDC)

An injury to the head arising from **blunt trauma**, **penetrating trauma**, **blast injury**, or some **external force (accelerating/ decelerating/ rotational) which can cause:** 

Decrease in consciousness Amnesia (loss of memory) Skull fracture An intracranial lesion Cognitive or focal deficits Death

#### Non-traumatic Brain Injury

#### Injury that occurs from a pathologic process

- Non-traumatic arteriovenous malformation (AVM) bleeds Stroke Cerebral Edema
- Intracranial lesion (GBM, metastases)
- Anoxic Encephalopathy





# Pathophysiology

#### **Primary Injury**

- Results from forces of impact, blast, or movement
- Direct disruption of the brain parenchyma from the shear forces
- Occurs immediately
- Not amendable to medical intervention
- Focal or diffuse
- Impact depolarization

Massive surge in extracellular potassium and glutamate release occurring after head injury and lead to secondary injury.

**\*\* EXCITATORY NEUROTRANSMITTERS** 



# Pathophysiology

#### **Secondary Injury**



Cascade of biochemical, cellular, and molecular events right after primary injury has taken place.

These involve:

- Delayed neuronal injury
- Inflammatory response
- Brain swelling
- Microvascular injury
- Ischemia
- Hypoxia
- Metabolic failure
- Elevated ICP decreased CPP
- Electrolyte imbalances









# content not available





O'Neil D, et. al. Front Pharmacol, June 2018









Slide from Giza C, Brain Injury Summit, 2018



### **Revised Neurometabolic Cascade**

ann





# Using Animal Models

Considerations for Experimental Animal Models of Concussion, Traumatic Brain Injury, and Chronic Traumatic Encephalopathy—These Matters Matter

Mark W. Wojnarowicz<sup>1</sup>, Andrew M. Fisher<sup>1,2</sup>, Olga Minaeva<sup>1,2</sup> and Lee E. Goldstein<sup>1,2,3\*</sup>



from texasvetpets.org

- 1. Clearly define human condition being modeled
- 2. Determine the purpose for using a particular model
- 3. Relate features of animal model with human condition
- 4. Translate/confirm animal findings in human subjects



ANIMAL MODELS

#### Dendritic Spine Loss and Chronic White Matter Inflammation in a Mouse Model of Highly Repetitive Head Trauma



Charisse N. Winston,\* Anastasia Noël,<sup>†</sup> Aidan Neustadtl,\* Maia Parsadanian,\* David J. Barton,\* Deepa Chellappa,\* Tiffany E. Wilkins,\* Andrew D. Alikhani,\* David N. Zapple,\* Sonia Villapol,\* Emmanuel Planel,<sup>†‡</sup> and Mark P. Burns\*

# Repeat mild TBI models

- -- 30x rmTBI causes white matter damage.
- -- 30x rmTBI does not cause synapse loss.
- -- 30x rmTBI does not cause learning or memory impairment.
- -- 30x rmTBI causes anxiety.







•There is a significant unmet need for management of concussion.

•Current standard of care (with controversy) is rest, analgesics or off label medications for headache, antidepressants and stimulant medications when needed.

•Estimated medical costs in the US is \$10-\$15 billion per year.





1. Relationship to post-concussive symptoms (cognitive dysfunction/impairments, headaches, balance deficits, others) and understanding timing may help guide expectations of recovery and planning of rehab.





1. Relationship to post-concussive symptoms (cognitive dysfunction/impairments, headaches, balance deficits, others) and understanding timing may help guide expectations of recovery and planning of rehab.





### 2. It Helps Explain Vulnerability to Second Insults

? Related to Second Impact Syndrome (SIS)







Glucose metabolism



2. It may help to explain vulnerability to second insult

Repeated Mild Traumatic Brain Injury: Mechanisms of Cerebral Vulnerability

👭 Memory



Prins ML, et al., J Neurotrauma 2013





2. It may help to explain vulnerability to second insult

	4 -	-		=			
Ke	peare	0 C	oncl	ISSIO	ns in	н	umans

No. of Previous No. (%) of Multiva Concussions Incident Concussions* Rate R	riate-Adjusted contatio (95% CI)†
0 122 (3.7) 1.0	with
1 41 (5.4) 1.4	(1.0-2.1) rate
2 15 (10.5) 2.5	i (1.5-4.1)
≥3 10 (12.7) 3.0	) (1.6-5.6) con

story of prior cussion associated a higher of sequent cussion.

<b>Table 4.</b> Length of Symptom Recovery in Players With Concussion by History of Concussion*									
		No. of Previous Concussions†							
Length of Symptom Recovery (d)	0 (n = 122)	1 (n = 41)	2 (n = 15)	≥3 (n = 10)					
Rapid (<1)	37 (30.3)	16 (39.0)	5 (33.3)	0					
Gradual (1-7)	76 (62.3)	19 (46.3)	7 (46.7)	7 (70.0)					
Prolonged (>7)	9 (7.4)	6 (14.6)	3 (20.0)	3 (30.0)					
*Data are expressed as No. (%	a) of players with concus	sion.							

Moreover, symptom duration was longer in those with more prior concussions.

+P = .03 by Fisher exact test.

#### Of in-season repeat concussions, 11/12 (92%) occurred within 10 days of initial concussion

Guskiewicz et al., JAMA 2003





# 3. It can help to determine when and/or how to activate the brain once injured.



Summit, 2018





# 4. Early pathophysiology may be associated with chronic degenerative changes

- Chronic Neurocognitive Impairment (CNI) static
- Chronic Traumatic Encephalopathy (CTE) progressive



# Classifications of TBI

Mild TBI (or Concussion)

- Glascow Coma Scale (GCS) 13-15
- Transient confusion, disorientation, or impaired consciousness
- Loss of Consciousness
  - 0-30 mins (having LOC is not a necessary criteria to have a TBI)
- Post traumatic amnesia
  - lasting from 0-24 hours
- Normal Brain imaging
  - Can still be considered mild if an intracranial process is shown on imaging. So long as other criteria are met



# Classifications of TBI

Moderate TBI

- GCS of 9-12
- Brain imaging can be normal or abnormal
- Loss of Consciousness
  - More than 30 mins and less than 24hrs
- Post Traumatic Amnesia
  - More than one day but less than 7 days



# Classifications of TBI

Severe TBI

- GCS of 3-8
- Brain Imaging may be normal or abnormal
  - Depends on the type of imaging (CT, MRI, DTI MRI)
- Loss of Consciousness
  - Greater than 24hrs
- Post Traumatic Amnesia
  - Greater than 7 days



# Post-concussion Syndrome (PCS)

Constellation of (sometimes) disabling symptoms

- Headache
- Dizziness/Imbalance (vestibular dysfunction)
- Cognitive dysfunction (difficulty with concentration/attention, forgetfulness, "fog")
- Neurobehavioral dysfunction (irritability, anxiety, depression)
- Vision changes (post-traumatic vision syndrome)
- Insomnia
- Fatigue
- Light and/or noise sensitivity

The frequency and natural history of the disorder is unclear, symptoms often persist for months, are resistant to treatment but eventually will lessen.

International Classification of Disease, 10<sup>th</sup> Revision, Criteria for post-concussion syndrome. Interval between head trauma with loss of consciousness\*\*\* and development of symptoms,<4wk

\*\*\* meh.



### Epidemiology

#### Incidence

#### CDC

# 2.87 million TBI-EDHDs annually (2014)

ED Visits, Hospitalizations, Deaths

288,000 were hospitalized and discharge alive

2.53 million were treated in ED the ED.

56,800 deaths

Moderate to severe TBI within 30 days 21 percent Severe TBI within 30 days 50 percent

These do not include

-Physician visits -Outpatient facilities -US military personnel

-Those that do not seek medical care.

\*\* There are likely over 300,000 cases additional





### Epidemiology

# Epidemiology

# Male:Female ratio

3:1

Mortality is 3-4 times greater in males

(will see age-related breakdown in a moment)

Ethnicity

Caucasians 66%> African American 22%> Hispanic 8% > Asian Americans (3%)

**Marital Status** 

Single > Divorced > Widowed/Separated > Married



# CONCUSSION IN SPORT GROUP

# **Brief History**

- Meetings: 2001, 2004, 2008, 2012, 2016
  - Aka, International Symposia on Concussion in Sport
  - Latest consensus statement in 2017
- Sports related concussion (SRC)
  - Unresolved: Reversible physiologic changes vs similar in TBI spectrum to severe TBI just to lesser degree
  - Numerous technical definitions
  - CISG: Consistent definition since 2000
  - "11 R's" : Recognize, remove, reevaluate, rest, rehabilitation, refer, recovery, return to sport, reconsider, residual effects and sequela, risk reduction



# Recognize

SIDELINE

- Detection/measurement devices
  - \*\* use not yet supported
    - No measurement of impact to brain itself
    - Inconsistent studies
  - Helmet-based
  - Video-based
  - Mouth guards
- Sideline:
  - Athlete should already be removed from play at this point, even if just temporarily
  - SCAT5 (Sports Concussion Assessment Tool v5)
  - CRT5 (Concussion Recognition Tool v5)
- RAPID SCREENING >> DEFINITIVE DIAGNOSIS





#### Next...

# Re-evaluate

# -ER

#### -PCP

# -Specialist

Not as common this early, but becoming preferred (this would usually come at "Refer" stage per CISG)

#### -Neuropscyhology

- Ideal vs location and system-dependent reality
- Impact, Moca, MMSE
  - Inherent limitations
- Determination of necessity for more urgent testing or treatment
- Future: advanced neuroimaging (e.g. DTI), biomarkers, etc.
  - Not adequately validated for clinic use at this time



# Concussion in Sport Group (CISG) - 11 R's

# Rest

Consensus? Rest until symptom-free

- Lack of evidence!
- Pathophysiology... activation...
  - at least 24-48 hrs of rest from most activities
- Case by case





### What We Do Here

# Rehabilitation

- CISG: very non-specific
- Again, timing?
  - Typically at least 2 weeks (most PCS symptoms to resolved in 10-14 with adequate rest and precautions)

- So now what?



# Rehabilitation

- THOROUGH Evaluation and Plan
- Interdisciplinary/Multidisciplinary Approach Licensed/Certified Athletic Trainer (LAT, ATC) Specialist MD/DO/PAC/APNP PCP PT SLP OT Neuropsychology Clinical Psychology/Psychiatry Nursing Neuro-optometry School FAMILY





The Fox Valley Concussion Program is a collaborative venture between Ascension and Neuroscience Group



# Multidisciplinary Rehab Approach



#### Rehabilitation

- PT:
  - Vestibular/balance rehabilitation
  - Oculomotor
  - Cervicalgia & Headache modalities
    - Craniosacral Therapy
- OT:
  - Oculomotor/Vision
  - Biofeedback, Relaxation & Stress Management Techniques
  - Driving Assessments
  - Cognitive rehabilitation
- SLP:
  - Communication & Cognitive Rehab (memory, concentration, problem solving, processing, communication disorders, etc.)
- Rehab Psychology
  - Supportive therapy
  - Anxiety, stress management
  - Trauma focused therapy
  - Cognitive behavioral therapy
  - Relaxation training & mindfulness





# Rehabilitation

- Recommendation:
  - Individualized plan
  - Ok to request consultation if uncertainty exists
  - Early intervention preferred, but starting in more subacute phase
  - Inter- or Multidisciplinary meeting and planning
  - Involvement of family, LAT, PCP





### Vision

- Vision screen should be routine on all new patients with any concern for visual, vestibular, or headache symptoms beyond 2-3 weeks (if warranted by exam).
  - ? Neuro-optometry
- Custom vision program
- Particular attention to previous visual aids
  - Is there a change following injury?
  - Increased risk of MVA, "pseuo-dyslexia", etc. if missed
  - Can be difficult with communication impairments









ACUTE treatments in the work (The race is on!)

- Amarantus
  - Developing MANF for mTBI
  - Not lipophilic difficult to pass the BBB
- Neuren
  - is developing an IGF-1 analog
  - Orally delivered no direct access to CNS
  - Worrisome side effects on unknown tumors (IGF-1 for 7-14 days might increase growth of subclinical, undiagnosed malignancy, e.g., in an elderly subject with a concussion)
- Oxeia Biopharmaceuticals
  - Orally delivered Mitochondrial drug with variable access to the CNS
  - Issues with weight gain, sparse data available
- Prevacus, Inc.
  - Lead molecule PRV-002 is a proprietary neurosteroid
  - Intranasal application



Fin.

