UPDATE ON CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

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Objectives

• Quick review of “what is a concussion.”
• Briefly review significant risk factors and current attempts to help prevent CTE (concussion management)
• Review the current status of CTE research.
• Identify some possible neurobehavioral correlates of CTE and needed cautions re: this area.
• NFL? NHL? Possible problems with retrospective analysis and post hoc reasoning
• More specific focus on the Sport Community
• First: we will review some basics of concussion -- to better understand, what WE BELIEVE to be some factors in the development of CTE
Gentlemen and Gentleladies,
This is a football
(To grossly generalize from the great Vince Lombardi)

- So: What is a concussion?
  - Concussion, or mild traumatic brain injury (mTBI):
  - “a complex pathophysiologic process affecting the brain, induced by traumatic biomechanical forces” (Aubry, et al, 2002)

- Mechanisms, or forces, that cause a concussion can be delineated as either:
  - Direct: e.g., a helmet to helmet collision involving direct contact with the head
  - Indirect: e.g., a whiplash, acceleration-deceleration type movement with no direct contact with the head

- Neuropsychological deficits may be evident even when no abnormalities are detectable on detailed neurologic or radiologic exams.

What Happens to Brain in Concussion?

- Stage 1: Concussion occurs:
  - The axons that carry impulses from neuron to neuron stretch unnaturally, garbling their signals
    - The neurons fire simultaneously, causing high action potentials. As they fire, Potassium (K+) rushes out and Calcium (Ca2+) rushes in, clogging the neurons’ mitochondria

- neuropsychologist David Hovda, UCLA's Brain Injury Research Center
**STAGE 2:** To fuel the absorption of new Calcium, the sodium & potassium (Na+ & K+) pumps work overtime to restore neuron potentials: so, the neuron consumes glucose.

- Metabolizing glucose creates lactate, that can damage cell walls. This creates hypermetabolism in the cell.

**STAGE 3:** The calcium-clogged mitochondria don’t get needed O₂. This causes a neuronal energy crisis. Blood flow drops and cells begin to die depending on severity of decreased cerebral blood flow.
Neurometabolic Cascade
Following Cerebral Concussion (animal model)

(Giza & Hovda, 2001)

DINGS?

“No I’ve never had a concussion before. I mean I’ve been ‘dinged’ a couple of times this season and pretty much most seasons, but never had any concussions; just little dings, but I’m OK to go back in after those.”

-20 year old NCAA football player
### Hallmark (?) Symptoms

- **LOC?!**
  - ~6-9% of concussed athletes experience LOC (Guskiewicz et al., 2003)

- **Post-traumatic amnesia (PTA)**
  - Better predictor of severity (Collins et al., 2003)

- **Headache**
  - ~70% \(^+(Lovell et al., 2004)\)
  - Better predictor of severity (Collins et al., 2003)

- **“Fogginess”**

- **“Dizziness”** better prediction of prolonged recovery (?Vestibular)

Sometimes symptoms do not present themselves for 24+ hours

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### Other Symptoms

(Pardini et al., 2004)

- **Somatic**
  - Nausea
  - Vomiting
  - ‘Foggy’, dazed feeling
  - Balance/coordination problems
  - Visual
  - Auditory

- **Affective/Emotional**
  - Sadness, depression
  - Anxiety and / or Panic Reactions* 
  - Labile affect
  - More emotional
  - Anger, hostility

- **Cognitive**
  - Disorientation
  - Confusion
  - Fogginess
  - Processing problems

- **Sleep Problems**
  - More or less
  - Trouble falling asleep
  - “Fitful” sleep (not rested)*

- **Behavioral**
  - Diet changes
  - Academic problems
  - Performance decrements in sport
  - Personality changes
  - Impulsiveness
  - Withdrawal/isolation


Note: CTE, as we will see, may share many of these symptoms, as they become chronic
Four Major Issues for the Management of Acute Concussion

1. Identify potential neurosurgical emergencies (Hemorrhage, Epidural, Subdural)
2. Prevention of catastrophic outcome related to acute brain swelling
3. Avoidance of cumulative brain injury possibly related to repeated concussion.
4. Assessment of neuropsychological deficits and educate the patient and families, and educators of how to manage & recover from deficits, including return to play decisions.
Newer Classification System

This system includes how it happens, and allows for evolution of the concussion from how it happens to how it evolves.

A Simple Concussion can become a Complex Concussion, and a Complex Concussion can become a simple concussion.

- **SIMPLE:** Athlete suffers an injury and immediately stops and is attended to. This generally resolves without complication over 7-10 days. Usually, no further intervention is required during the period of recovery. REST!
- **COMPLEX:** Athlete suffers several concussions in succession, numerous subconcussive blows, or continues play after a concussion, and/or prolonged LOC >1 Min. Will experience persistent symptoms including symptom recurrence with exertion, ongoing sequelae, or prolonged cognitive impairment following the injury. Formal neuropsychological testing and other investigations should be considered. Multidisciplinary management is often needed.

Neuropsychological (NP) Testing

- Neuropsychological testing is an objective method for determining subtle cognitive changes
- Effective for detecting lingering deficits following a concussion
- Allows for individual variation, management
- Computerized, serial testing
- Sometimes more extensive testing is needed
  - 24-72 hrs, 5-10 days
  - Symptom free, back to baseline
Return to Play Issues

- When to return?
  - Asymptomatic
  - Back to baseline (if NP testing involved)
- Disqualification
  - Competition
  - Season
  - Career
- Sport Psych referral-?
- Individual decision based on ALL available information

Zurich Concussion Conference: Return to Play Recommendations

1. Removal from contest following any S/S of Concussion (especially for High School Students)
2. No Return to play in current game (Used to allow return after 15 mins. 0 symts)
3. Medical evaluation following injury
   a. rule out more serious intracranial pathology
   b. Neuropsychological Testing considered “cornerstone” of proper post-injury assessment
4. Stepwise return to play
   a. No activity and rest until asymptomatic
   b. Light aerobic exercise (“Non-Pounding”)
   c. Sport-specific training (“Pounding” aerobic activity)
   d. Neuropsychological Re-evaluation*** (Hogue Add on to guidelines)
   e. Non-contact drills
   f. Full-contact drills
   g. Game play
Consensus Regarding Management

• Graded Return to Exertion
  - Consider physical AND mental exertion
• Return to play must be a case by case decision
  - All data are important to decision
  - Resolution of symptoms and NP
• Age and # of injuries need to be considered
• How were they managed?
• Long term monitoring, follow-up and treatment necessary for PCS
  - More follow-up with ‘resolved’ athletes
  - Sport Psych/Psych of Injury referral

Beliefs:

• It is most of our collective beliefs, that the current theories and management steps are sufficient to negate the possibility of cumulative effects of concussions.
• Most working within the sporting field feel confident that when the current guidelines are followed, that the MAJORITY of athletes or others sustaining concussions will have full recovery of functions.
• Further, poor management of concussion increases the probability of layered concussions creating cumulative injury and more permanent cell death, and compromised function.
• In all honesty, there is much that we don’t know.
  - the “concussion-prone” athlete
  - those that seem “resistant” to normal recovery protocols.
  - Are these current protocols sufficient answers to the possible development of CTE?
What is CTE?

• First associated with Harrison Stanford Martland: describing the clinical features of a neuropsychiatric syndrome affecting pugilists (professional boxers). First recognized in 1928.
• This was known as “punch drunk” or, “dementia Pugilistica”
• Gradually recognized in range of people with exposure to repetitive brain trauma: physical abuse, head banging, poorly controlled epilepsy, dwarf-throwing, and rugby.
• Recently: associated with modern contact and collision sports, including American football, soccer, baseball, wrestling, ice hockey, and military personnel exposed to RHI during military service, including explosive blasts
• Made “famous” by Dr. Bennet Omalu when autopsied brain of Mike Webster from Pitts. Steelers in 2002. (50 y.o. man). “League of Denial: inside the NFL’s Concussion Crisis” PBS documentary (2013). Recent Concussion movie, with Will Smith
• Dr. Ann McKee; Boston Brain bank. 2011 Multidisciplinary Concussion Summit @ EUP.
What is CTE?

- Chronic Traumatic Encephalopathy is a unique neurodegenerative tauopathy characterized by a pathognomonic lesion. The pathognomonic lesion consists of a perivascular accumulation of abnormally hyperphosphorylated tau in neurons and astrocytes distributed in an irregular fashion with a propensity for sulcal depths of the cerebral cortex.

It is Asserted: CTE is a unique neurodegenerative disorder that occurs as a latent consequence of cumulative repetitive head impacts (RHIs), including concussion and subconcussion.
Current level of diagnosis

- Only diagnosed after death by neuropathologic examination
- Precise incidence and prevalence of CTE is still unknown.
- Large-scale, longitudinal prospective studies are needed to directly address public concerns and close existing gaps in the basic and clinical science related to natural history, evaluation, and management, and long-term effect of RHI exposure.*
- Neuropathology of CTE is “increasingly well defined.”
- 2013, in largest case series study: McKee and others looked at 68 males with exposure to RHI; ranging from ages 17-98 (mean 59.5 yrs.). In young: mildest form—
  - Focal perivascular epicenters of hyperphosphorylated tau (p-tau) immunoreactive neurofibrillary tangles (NFTs) and astrocytic inclusions found clustered at the depths of cortical sulci.
  - Severe Dz: profound tauopathy- widespread regions. Other abnormalities (advanced dz) included abnormal deposits of phosphorylated TAR DNA-binding protein (TDP-43), neuroinflammation, varying amounts of beta amyloid plaques, neuronal loss, and white matter degeneration.


Current level of diagnosis

- Based on this, they developed preliminary criteria for dx. And a 4-tiered staging system for grading pathologic severity were proposed.
- In 2015, a series of consensus panels came together to define the neuropathological criteria for CTE, with trials of blinded evaluations of 25 cases of various tauopathies, including CTE, Alzheimer's disease, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, primary age-related tauopathy, and parkinsonism dementia complex of Guam; without knowledge of age, sex, athletic history, clinical symptoms, or gross neuropath. Findings.
  - Results were “good” agreement among the neuropathologists, and better agreement between reviewers and the dx of CTE.
- Furthermore, the panel refined the preliminary criteria and defined CTE as a distinctive disease with a pathognomonic lesion of abnormal tau in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci and in an irregular pattern.

**Current level of diagnosis**

**STAGING**

**Stage I:** P-tau is restricted to isolated foci in cortex; focal lesions are perivascular accumulations of p-tau; astrocytic inclusions, NFTs and dot-like structures.

**Stage II:** Multiple P-tau lesions at depths of cerebral sulci.

**Stage III:** P-tau pathology is widespread in cortex, amygdala, hippocampus, & entorhinal cortex shows neurofibrillary pathology.

**Stage IV:** Severe pathology is widespread in cortex and medial temporal lobe, and sparing of calcarine cortex.

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**Current levels of diagnosis**

Gross Pathology: Moderate to severe CTE:
1. Cavum septum pellucidum and septal fenestrations
2. Reduced brain wt and cerebral atrophy; typically bilateral and more severe in frontal and medial temp. lobes: hippocampus, amygdala, & entorhinal cortex
3. Thalamic & hypothalamic atrophy... incl. Mammillary bodies
4. Thining of corpus callosum, espec. in posterior isthmus
5. Ventricular dilation; disproportionate in 3rd ventricle
6. Depigmentation of the locus coeruleus and substantia nigra

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1. Corpus callosum is thinned
2. The septum pellucidum, normally a thin membrane that divides the two sides of the brain, is torn
3. The frontal region of the brain shows atrophy
4. The temporal region of the brain, including the hippocampus, shows shrinkage
Some Prevalence Data

*National Institute of Neurological Disorders and Stroke

**listed as: rugby, soccer, CRICKET?, lacrosse, judo, and SQUASH?*

- NINDS* criteria, Bieniek and colleagues (2015) reviewed clinical records and brains of 1721 cases donated to Mayo Clinic Brain Bank over 18 years.
  - 32% of contact sport hx. athletes had evidence of CTE
  - Also means: 68% of those in contact sport did NOT
  - No cases of CTE in 162 “control brains” w/o hx trauma, or in 33 cases w/o single TBI
  - ONLY 21 cases with CTE pathology, and 19 of those had participated in football or boxing, many were multisports athletes including rugby, wrestling, basketball, and baseball. One athlete played only baseball, and one other only basketball.

- Queen Square Brain Bank: CTE in 11.9% of neurodegenerative d/o, & 12.8% elderly controls. Cases with CTE, 93.8% had a history of TBIs; 34% participated in “high risk collision sports”** & 18.8% were military veterans

Differentiation and Clinical Presentation

- Beta-amyloid (Aβ) plaques are found in 52% of CTE, & are significant with aging. Aβ in CTE, when they occur, are typically less dense than in Alzheimer Disease and predominantly diffuse.
- Clinical presentation is “typically in 1 or more of 4 domains:”
  - Mood
  - Behavior
  - Cognitive
  - Motor
Clinical Presentation

- Behavioral symptoms of CTE have been said to include explosivity, verbal and physical violence, loss of control, impulsivity, paranoia, and rage behaviors.
- Behavioral symptoms of Anabolic steroid abuse: idem.
- Behavioral symptoms of some frontal dementias and some other neurodevelopmental disorders: idem.
- Behavioral symptoms of some Adult ADHD, LD, Personality Disorders: idem.

Attempts at defining Clinical Signs and CTE

- Montenigro et al (2014) attempted to subtype numerous possible symptom clusters by reviewing 202 published cases. They proposed “research criteria” for Traumatic Encephalopathy Syndrome (TES).
- This consists of four variants
  - TES behavioral/mood, TES cognitive, TES mixed, and TES dementia
  - Also: classifications of: Probable CTE, Possible CTE
  - Are stated as “not meant to be used for a clinical diagnosis. Rather, they are to be viewed as research criteria that can be employed in studies of underlying causes, risk factors, differential diagnosis, prevention, and treatment of CTE and related disorders”*
<table>
<thead>
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<th>Mood features</th>
<th>Cognitive features</th>
<th>Motor features</th>
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<tbody>
<tr>
<td>Explosivity</td>
<td>Depression</td>
<td>Dementia</td>
<td>Ataxia</td>
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<td>Loss of control</td>
<td>Hopelessness</td>
<td>Memory impairment</td>
<td>Dysarthria</td>
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<td>Short fuse</td>
<td>Suicidality</td>
<td>Executive dysfunction</td>
<td>Parkinsonism</td>
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<td>Impulsivity</td>
<td>Anxiety</td>
<td>Lack of insight</td>
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<td>Aggression</td>
<td>Fearfulness</td>
<td>Perseveration</td>
<td>Tremor</td>
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<td>Rage</td>
<td>Irritability</td>
<td>Impaired attention and</td>
<td>Masked facies</td>
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<td>Labile emotions</td>
<td>Concentration</td>
<td>Rigidly</td>
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<td>Apathy</td>
<td>Language difficulties</td>
<td>Muscle weakness</td>
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<td>Inappropriate speech</td>
<td>Loss of interest</td>
<td>Dysgraphia</td>
<td>Spasticity</td>
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<td>Fatigue</td>
<td>Alogia</td>
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<td>Insomnia</td>
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<td>Mania</td>
<td>General cognitive impairment</td>
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<td>Euphoria</td>
<td>Reduced intelligence</td>
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<td>Paranoid delusions</td>
<td>Mood swings</td>
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<td>Angst</td>
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<td>Psychosis</td>
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<td>Social isolation</td>
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Correlation vs Causation

- Askins, et. Al. presented a cautionary review of other factors that may be influencing CTE Clinical Correlates
- Cognitive, Emotional, Behavioral Changes of CTE
  - Developmental and demographic factors
  - Neurodevelopmental disorders
  - Normal Aging
  - Adjusting to Retirement
  - Drugs and Alcohol Abuse
  - Surgeries and Anesthesia
  - Sleep Difficulties

Cognitive

- When the brain of a deceased athlete shows CTE, there is an assumption to attribute all reported problems to the CTE

Emotional

- These attributions are premature & neglect
  - Other biological, psychological and social factors that may produce some or MANY of the symptoms associated with CTE

Behavioral

- Firm support for Cause/Effect relationships is lacking
  - Iverson (2014) contested the link of CTE and suicidality.
  - Suicide in retired NFL players is SIG. lower than gen population
  - In the above, mentioned Traumatic Enceph. Synd., any pt. with dx of dementia if in collision sport would qualify for “probable TES” “Possible TES” is even more inclusive
Neurodevelopmental

- LD, ADHD = 13.5% college athletes
- Historical for rage, impulsivity, and mood disorders
- When they get older, it doesn’t get better
- Impaired cognition on diagnostic tests
- Take longer to recover from concussion
- SOME suggestion of predisposal to neurodegenerative diseases.
- Golimstock reported 47.8% of Diffuse Lewy Body (DLB) cases had preceding ADHD symptoms: carried a 5.1X increased risk of developing DLB compared to controls.
- Cognitive Reserve theory suggests prior neural neurodevelopmental issues MAY predispose those to be less able to negotiate aging or injury related neurological changes.
- Stamm (2015) reported “effects of repetitive TBI”: compared neuropsych profiles of retired American Football players before age 12, to those who played later: worse in reading accuracy, verbal memory, and exec. functioning. BUT: were group diff. with LD dx.
Drugs and Alcohol

- Overuse of prescription medications (often associated with chronic pain), alcohol abuse, and use of steroids may all have negative effects on the neurobehavioral profiles of active and aging athletes.
- Prescription and nonprescription drug use is highly prevalent at many levels of athletic participation (Alaranta et al. 2008; Warner et al. 2002).
  - Narcotic analgesics, antiinflammatory drugs were prescribed @ VERY high Freq.
  - Lawsuits against NFL for this…. Toradol, Percocet
  - Cottler (2011) reported 52% of NFL athletes used prescription opioids and majority reported misuse (37% admitted to misuse)
  - Strogest predictors of overuse were self-reported undiagnosed concussions, having 3 or more injuries, and being an offensive lineman.
  - 80% of retired NFL athletes report persistent daily joint pain, and consequent retirement problems due to this (lack of exercise, weight gain, sleep problems, difficulty transitioning to “life”)

Drugs and Alcohol

- Opioid dependent individuals report higher levels of depression, anxiety, apathy, and explosiveness than non-users.
- College athletes report higher incidence of binge drinking than non-athlete students.
- Alcohol misuse:
  - associated with a number of neurocognitive and other health consequences both acute & chronic.
  - Direct neurotoxic effects of alcohol include depression of CNS activity, reduced cerebral blood flow, and blood-brain barrier dysfunction (Alexander et al. 2004; Haorah et al. 2005; Shih et al. 2001).
  - Heavy use in older populations associated with 22% risk of dementia.
- Anabolic-androgenic steroids (AAS) prevalence in professional football players reported (uner-reported) @ 9.1%.
- Even small amounts suggest cell death of neuroblastoma and mammalian cells. Also, see reduced amygdala functions.
- Confusion, memory problems, lack of inhibitory control are commonly reported including irritability, impulsivity, mood swings, aggression, and violence as well as depression.
**Summation**

- Evaluating premorbid neurobehavioral functioning is essential to understanding individual specific change over time.
- Considering a broader biopsychosocial explanatory framework that includes other potential explanations of the complex symptom picture is important.
- Failed to even touch on HUGE implications of retirement, including transitioning into post-career roles, fact that many are in poor financial shape (78% experience financial distress within 2 years after retirement), significant drug and alcohol abuse, and shifts in personal identity and all factors that create increased stress and strain can have direct and indirect factors associated with CTE behavioral correlates.
- Numerous surgeries, and theories regarding acute and chronic post-operative Cognitive dysfunction, not to mention acute and chronic sleep disturbances.

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**Mark Kelso: the ”Bubble Boy”**
At long last: Public Opinion & why we need to be thoughtful

The NHL Weighs in

N.H.L. Commissioner Gary Bettman Continues to Deny C.T.E. Link

By JOHN BRANCH  JULY 26, 2016

N.H.L. Commissioner Gary Bettman said, “the relationship between concussions and the asserted clinical symptoms of CTE remains unknown.” Brad Penner/ Getty Images
• “The science regarding C.T.E., including on the asserted ‘link’ to concussions that you reference, remains nascent, particularly with respect to what causes C.T.E. and whether it can be diagnosed by specific clinical symptoms,” Mr. Bettman wrote.

• He added: “The relationship between concussions and the asserted clinical symptoms of C.T.E. remains unknown.”

• Mr. Bettman repeatedly blamed the media for spreading the fear of C.T.E., and accused the plaintiffs in the concussion case for a public relations assault on the topic. He ended the letter by retelling the story of the former N.H.L. player Todd Ewen, who died of a reportedly self-inflicted gunshot wound last year at age 49. He was the latest in a string of former enforcers, including Boogaard, Bob Probert, and Wade Belak—all died young after displaying symptoms “related to CTE.”

• Unlike some of the other brains posthumously examined, however, Ewen’s did not show signs of C.T.E. That surprised Ewen’s wife, who said she hoped that others would take comfort that C.T.E. might not always be the culprit of a loved one’s unraveling. Mr. Bettman saw that as proof that public opinion had gotten unreasonably ahead of science.
• “These results indicate that in some athletes, multiple concussions do not lead to the development of C.T.E.” said Dr. Lili-Naz Hazrati, the neuropathologist who conducted the autopsy. “Our findings continue to show that concussions can affect the brain in different ways. This underlines the need to not only continue this research, but also be cautious about drawing any definitive conclusions about C.T.E. until we have more data.”

Finally:

• Dr. McKee’s research suggests that there is a link between multiple concussions, and possibly poorly managed concussions that have been layered one upon the other (possibly including sub-concussive blows).
• The “causal link” has yet to be demonstrated, and the research is currently in nascent stages.
• CTE can only positively be demonstrated by posthumous examination
• Clinical correlates overlap with many psychological and other neurodegenerative disorders that may inaccurately give one the impression that CTE has developed.
• Great caution is needed in over-attribution of “clinical signs and symptoms.”
• Examinations need to include muti-disciplines including extensive neurology, and neuropsychological examinations, extensive history gathering including learning disorders, more accurate account of concussions and management, and other factors related to “clinical presentation.”
Partial Reference List


