WHAT WE DO AND DON’T KNOW ABOUT THE LONG-TERM EFFECTS OF CONCUSSIONS

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2017 WSATA CONCUSSION SYMPOSIUM
DO CONCUSSIONS HAVE LONG TERM CONSEQUENCES?

• Huge media interest in long term effects
  • Neuropsych disorders, CTE, mood changes, suicide

• General view of concussion broadened
  • Attempts to understand injury effects across lifespan
  • What happens down the road?

• As health care professionals, we have a responsibility
  • Much of the debate is played out in mainstream media rather than scientific journals
"The trouble with quotes on the Internet is that you can never know if they are genuine."

- Abraham Lincoln
WHAT IS CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)?

- Progressive neurodegenerative disease, with associated cognitive, behavioral, and neuropathological findings
- Diagnosed only at autopsy
- Tauopathy, distinct from Alzheimer’s and other forms of dementia
- Separate from post-concussion syndrome
- Behavioral and neuropsychiatric issues predominate
- Dementia manifests late in the disease
- *Important area that needs further study*

CTE

• Origins of CTE
  • Case report by Omalu
  • Diffuse amyloid plaques and neurofibrillary tangles and tau-positive neuritic threads in neocortical areas
  • Concluded potential long term neurodegenerative outcomes in retired NFL players subjected to repeated mild TBI

• Need to pay attention to other risks to the structural integrity of the brain
  • Think more of “the nature of the brain which was injured, than the nature of the brain injury”
    – Carson A 2017
CTE
HISTOPATHOLOGY

- Irregular, multifocal, and generally perivascular tau-immunoreactive neurofibrillary tangles
  - Pathognomonic finding exclusive to CTE distinguishing it from other neurodegenerative diseases

  Omalu B et al. Neurosurgery 2011;173-183

- Large population studies reviewing pathological findings in the general population show that neurodegenerative pathological changes similar to CTE can occur naturally with the aging process.
NEUROPATHOLOGIC STAGES

• I: p-tau perivascular foci in depths of cortical sulci

• II: spread to superficial layers of adjacent cortex

• III: widespread throughout frontal, insular, temporal and parietal cortices

• IV: most of the cerebral cortex and medial temporal lobe
Athletes with significant neurological decline do not always have histopathological changes of CTE.

The presence of histopathological changes of CTE are not always associated with neurological symptoms.

- McKee AC et al. Brain 2013;43-64
- Smith DH et al. Nat Rev Neurol 2013;211-221
GROSS PATHOLOGY OF CTE

Gross Pathology

- May be normal despite extensive microscopic damage

- In advanced cases
  - Cerebral atrophy
  - Medial temporal lobe atrophy
  - Mammillary body atrophy
  - Thinning of the hypothalamic floor
  - Marked dilation of ventricles
  - Cavum septum pellucidum
  - Pallor of the substantia nigra

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CTE
CLINICAL PRESENTATION

Initial Clinical Presentation
– 8 to 10 years after experiencing head trauma
– Mood and behavior problems
  • Irritability
  • Impulsivity
  • Aggression
  • Depression
  • Short-term memory loss
  • Suicidal

Late Stage Clinical Presentation
– Cognitive and motor impairment
  • Dementia, gait and speech abnormalities, parkinsonism
    – McKee AC et al. Brain 2013;43-64
    – Stern RA et al. Neurology 2013;1122-1129
Many of the early clinical features of CTE are indistinguishable from depression

- Sadness
- Hopelessness
- Cognitive difficulties

Men with depression more likely to engage in risky behavior and be angry, irritable, and aggressive

Depression and chronic pain both increase risk for suicide
HOW COMMON IS CTE?

- Autopsy diagnosis
  - Cannot determine incidence and prevalence
  - Cannot determine causation

- Limited data on epidemiology of repetitive concussion

- Number of cases in the medical literature of CTE (confirmed by neuropathology) from the first published case in 1954 to 2013
  - 153 by 2013. Many overlapping publications
  - Initially all male
  - 4 additional cases? Numbers vary. Likely less than 200 total cases
  - 2 female cases?
    - McKee and Robinson 2014
“CTE has received widespread media attention and is treated in the lay press as established disease, characterized by suicidality and progressive dementia.”

“Currently no controlled epidemiological data to suggest retired athletes at increased risk for dementia or that they exhibit any type of unique neuropathology. Remain no established clinical or pathological criteria for diagnosing CTE. Until further controlled studies are completed, it appears to be premature to consider CTE a verifiable disease.”

Randolph, C. Current Sports Medicine Reports 2014; 33-37
• Premature to suggest that contact sport retirees are at risk for CTE

• Potentially dangerous
  • This type of information may lead individuals experiencing depression to misinterpret their symptoms as being the first stages of a fatal neurodegenerative disorder
“When a previously undescribed condition, such as modern CTE in retired athletes, is proposed based on neuropathological findings in a small and potentially biased sample, then the complex genetic and environmental variables (as well as the normal range of age-related brain degeneration) implore us to cautiously review the data. There is insufficient evidence to establish a causal relationship between sports participation and the existence of modern CTE.”

Davis GA, Castellani RJ, McCrory P. *Neurosurgery* 2015; 1–
• Distinct tauopathy with an unknown incidence in athletic populations

• Cause and effect relationship has not yet been demonstrated between CTE and concussions or exposure to contact sports

• Interpretation of causation in the modern CTE case studies should proceed

• Important to address the fears of parents/athletes from media pressure related to the possibility of CTE

• Long-term longitudinal studies needed
  – Incidence and prevalence
  – Determine if progressive or reversible
  – Determine factors that can predispose

• Pathologic-clinical correlations
  – Need to establish and define links
  – Reproducibility across multiple investigators

• Development of antemortem tests
  – Biomarker
  – Imaging

McCrory P et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012
DO CONCUSSIONS HAVE LONG TERM CONSEQUENCES?

• Guskeiewicz 2005
  – Survey of retired NFL players (2552)
  – Cohort averaged 54 yo and 6.6 yrs pro experience
  – General health survey
  – Questionnaires on memory and issues related to MCI completed by subset of 758 players

• Those with 3 or more reported concussions
  – 5-fold greater prevalence of MCI
  – 3-fold greater prevalence of reported memory problems

Guskiewicz 2005
PROBLEMS WITH SURVEY RESULTS

• Survey results depended on retrospective reports and self reports of chronic symptoms
  • Without formal evaluation or medical documentation
  • Selection bias

• Prompted speculation about long-term risks of repetitive concussions

• Authors called for prospective, longitudinal studies

• Set in motion new line of research

Guskiewicz 2005
Lehman studied rates of neurodegenerative diseases in 3439 retired NFL players.

Neurodegenerative mortality of this cohort 3x higher than general population; AD and ALS was 4x higher.

Claim is based only on 17 cases.

All cause mortality of these NFL players (334 deaths) showed overall mortality was significantly reduced (half the SMR compared to national average).

To put this another way, “If football were viewed as a drug, it saved 296 lives but at the cost of 17 deaths”

-Carson 2017
• Cohort of 45 retired NFL players

• Evaluated relationships between
  • 3 neuroimaging parameters (cavum septum pellucidum, global mean score fractional anisotropy, microhemorrhages)
  • Neuropsych testing
  • Symptom and depression scales

• Did not see statistically significant correlation

• Conclusion
  • Associating the severity of structural brain changes to neurocognitive performance and symptoms burden after RBT is complex, may involve other moderating variables and demands further study
DOES PLAYING YOUTH SPORTS CAUSE CTE?

• > 7.8 million high school students (over 3.3 million girls and 4.5 million boys) participated in sports during the 2015-2016 school year (NFSH)

• There have been < 7 potential cases of CTE in high school athletes ever published
  • Incidental findings?
  • Too early to tell?

• “In paediatric populations, particularly young athletes, the effects of single or repetitive concussions on the risk of later-life neurodegeneration and dementia are unknown”

• National Federation of State High School Associations Participation Data. www.nfhs.org/content.aspxpx?id=3

• Love S, Solomon GA AJSM  http://ajs.sagepub.com/content/early/2014/06/05/0363546514535187

HIGH SCHOOL FOOTBALL AND RISK OF NEURODEGENERATION

• Evaluated long term outcomes of HS football players

• Rochester Minnesota high school football players 1946 to 1956 (438)

• Rochester Minnesota high school male band, glee club or choir club members (140)

• Record-linkage system of Rochester Epidemiology Project

• Looked for later development of dementia, Parkinson’s disease (PD), or amyotrophic lateral sclerosis (ALS)

Median follow up 50.2 years for football players and 59.1 years for the band/glee/choir members.

Football players showed no increased risk of dementia, PD or ALS.

Equipment, spearing, attention to concussions.

• New study that mirrored previous investigation
• Cohort of football players between 1956-1970

• Rochester Epidemiology Project
• Again assessed whether football players (296) had increased risk of neurodegenerative diseases later in life
• Non football playing male swimmers, wrestlers, and basketball players (190)

• Found no increased risk of neurodegenerative disease
  • Including dementia, parkinsonism, ALS
LONG-TERM EFFECTS OF ADOLESCENT CONCUSSION

• Evaluated potential long-term effects of adolescent concussion on cognitive and motor performance across lifespan

• 30 adults with history of adolescent concussion and 53 without history of concussion split into 3 groups
  • 18-30 yo (43)
  • 40-50 yo (18)
  • >60 yo (22)

• Participants completed computerized neurocognitive assessment and motor tasks
• Age significant effects on neurocognitive and motor tasks
  • Age had a consistent adverse effect on cognitive and motor performance

• Failed to identify any effect of adolescent concussion history on cognition or motor performance with age

• Longitudinal investigations still needed
Surveys of retired professional athletes
  - Positive association between the number of concussions and risk for depression

Minimal research on the relationship between multiple concussions and suicidal thoughts and behaviors.
• Cohort study of 3439 NFL players with at least 5 credited playing seasons between 1959 and 1988

• Standardized mortality ratios (SMRs) with vital status updated through 2013

• Suicide among this cohort of professional football players was less than half (SMR=0.47) compared to U.S. population of men stratified by age, race and calendar year

• No significant differences in suicide mortality between speed and non-speed position players

ADDITIONAL FACTORS CONTRIBUTING TO NEURODEGENERATION

• Reviewed factors, in addition to repetitive brain trauma, that may contribute to symptoms associated with CTE

• Described cognitive, emotional, and behavioral changes associated with
  • Developmental and demographic factors
  • Neurodevelopmental disorders
  • Normal aging
  • Adjusting to retirement
  • Drug and alcohol abuse
  • Surgeries and anesthesia
  • Sleep difficulties

• Evaluated these factors and the risk for developing dementia related neurodegenerative disease

• Repetitive brain trauma cannot be considered sole causative factor in development of CTE symptoms
  – Additional risk factors
  – Individual differences

Factors Influencing Clinical Correlates of CTE: A Review
Asken. Neuropsychol Rev 2017
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Asken Neuropsychol Rev 2017
DO CONCUSSIONS HAVE LONG TERM CONSEQUENCES?

- Current state of science on potential long-term risks

- Severe TBI elevates risk of Alzheimer disease \text{Guo 2000}

- Remains unclear if AD risk is seen in milder forms of TBI such as SRC

- No prospective, longitudinal studies of well defined cohorts over long periods of time have been conducted to determine if multiple concussions early in life affect risk for late life cognitive problems

\text{Long-Term Cognitive and Neuropsychiatric Consequences of Repetitive Concussion and Head Impact Exposure. McAllister, McCrea 2017}
• Literature limited to case studies or small case series

• Often rely on subjective and retrospective reports of family members regarding observed cognitive changes

• Lack objective measures of cognitive functioning

• Do not allow detailed characterization of impairments

• Difficult to tease apart factors principally contributing to cognitive decline
Further research required to answer fundamental questions to better understand effects of repetitive neurotrauma

- What are the true, population based risks?
- Who is at risk and why?
- Which factors predict an athletes risk?
- How can risks be modified to improve safety at all levels?
What is known and unknown?

Correlation does not equal causality

Large number of players, small number of CTE
  • There are other factors involved

Review of available evidence suggest that it is unknown if concussion is a risk for neurodegenerative disease

Need to recognize multitude of confounders that may cause neurodegeneration
  • Studies must control for Etoh/substance abuse, PEDs, psychological disorders, genetics, etc.

Understanding potential evidence based risks and benefits of being a professional NFL player
  • Results in increased life expectancy
  • Player education on retirement

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• Literature inconsistent

• More to learn about potential cause and effect relationships of repetitive head impact and concussion

• At this point unknown if concussion or subconcussive impacts cause CTE

• Designed research on long term consequences needed

• Future studies
  – Determine potential genetic predispositions
  – Determine if condition is progressive given certain modifiers

• Need for prospective, longitudinal, population-based studies

-Consensus statement on concussion in sport – The 5th international conference on concussion in sport held in Berlin
THANK YOU