Chronic Traumatic Encephalopathy in 2016: What We Know and What We Need to Know Next

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Disclosures

- Psychological Assessment Resources, Inc. (Royalties for Published Tests)
- Avid Radiopharmaceuticals (Funded Research Investigator)
- Amaranthus Bioscience (Funded Research)
- Amaranthus Bioscience (Medical Advisory Board Member)
- Avanir Pharmaceuticals (TBI Advisory Board Member)
- Biogen (Alzheimer’s Medical Advisory Board Member)
- I am a football fan

Great Strides in Sports Concussion Awareness and Management

Disclosures - Continued

- I know very little about concussions!
  - My area of expertise is neurodegenerative disease
- I’m not very concerned about concussions when it comes to later life brain disease
Concussions may be the Tip of the Iceberg

Repetitive Head Impacts
Moderate-to-Severe TBI
Symptomatic mTBI/Concussion
Subconcussive Trauma
**Subconcussive Blows**

- Impact to brain with adequate force to have an effect on neuronal functioning but No Immediate Symptoms of Concussion
- Some sports and positions very prone
  - Football linemen may have 1000-1500 of these hits per season, each at 20-30 g.
  - Double the number for the athletes who plays both offense and defense
  - Soccer heading = ~15 g also 1000+ per season.

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**Force = Mass x Acceleration**

- Athletes are getting bigger and faster!
  
  — Anzell et al., 2013

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**Subconcussive Blows**

- Broglio and colleagues (2011) found that high school football players received, on average, 652 hits to head in excess of 15 g of force. One player received 2,235 hits!
- Growing evidence that even after one season, repetitive subconcussive trauma can lead to cognitive, physiological, and structural changes.
  - Talavage et al., 2011
  - McAllister et al., 2012
  - Koerte et al., 2012, 2014
  - Pasternack et al., 2014

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**Do Concussions and Subconcussive Trauma Lead to Neurodegeneration?**
We Have Known About the Long-Term Consequences of Repetitive Head Impacts in Boxing for a Long Time

• Punch Drunk: Martland, 1928
• Traumatic Encephalopathy: Parker, 1934
• Dementia Pugilistica: Milspaugh, 1937
• Chronic Traumatic Encephalopathy: Bowman & Blau, 1940; Critchley, 1957

CTE in American Football

• "It is doubtful, in my opinion, if the benefits derived from playing this game, which I am free to acknowledge are very considerable in some directions, are commensurate with the risks it entails to life and limb -- which, according to statistics, are much greater than commonly supposed."

• West Point surgeon P.F. Harvey
• The New York Times, Nov. 18, 1893

CTE in American Football

• 1933: Homeopathic Medical Society of the State of Pennsylvania
  – first case reports of Punch Drunk dementia amongst football players
  – including one who “forged checks and did things suggesting the behavior of psychopathic personality” and the “condition we sometimes find in pugilists… pummeled about the head”

CTE in American Football

• 1937: Frank Scully, a former Columbia University football star
• Tracked down former teammates and uncovered varying degrees of “dementia, vagrancy, and motor deficiencies” in seven of his classmates
CTE in American Football

- 1980’s-2000’s: The *Cover-Up Period* brought to you by the NFL’s MTBI Committee
  – *Dr. No (Dr. Ira Casson) - 2007*

Long-Term Consequences of Repetitive Head Impacts in American Football

- First American Football Player with Neuropathologically Diagnosed Chronic Traumatic Encephalopathy
  – Omalu et al., 2005
  – Mike Webster, died in 2002
  – Began increased media attention to CTE

Chronic Traumatic Encephalopathy is Dementia Pugilistica

- Neurodegenerative disease, similar to Alzheimer’s disease but is a unique disease neuropathologically and clinically
- Believed to be caused, in part, by repetitive brain trauma, including concussions and subconcussive blows
- The repetitive trauma appears to start a cascade of events in the brain that eventually leads to progressive neurodegeneration

Chronic Traumatic Encephalopathy (CTE) *What we Know:*

- Not prolonged post-concussion syndrome
- Not the cumulative effect of concussions
- The disease appears to begin earlier in life, but the symptoms begin years or decades after the brain trauma and continue to worsen
CTE

• Like Alzheimer’s and other neurodegenerative diseases, CTE can currently only be diagnosed postmortem
• Dr. Ann McKee has examined more brains with CTE than any other neuropathologist; BU has the largest CTE brain bank (BU RHI Brain Bank) in the world
  – >250 brains examined

CTE Neuropathology

• Stay Tuned for Dr. Keene
• Characterized by abundance of a misfolded, hyperphosphorylated form tau:
  – Neurofibrillary tangles and astrocytic tangles
  – Marked neuropil thread pathology
  – Numerous p-tau positive “grains” in cortex and white matter suggestive of retraction blubs (morphological hallmark of lesioned axons).
• Pathognomonic findings of CTE:
  – Early perivascular distribution of tau
  – At the depths of cortical sulci
• Later widespread distribution; “prion spread”?

Unique Pathology of CTE

What we Know:

Perivascular

Tissue stained for hyperphosphorylated tau = brown

Depths of the Sulci
First BU CSTE NFL Case

All cases being presented are with the knowledge and approval of the individuals' family members.

John Grimsley - Died at Age 45
- Houston Oilers 1984-1990; Miami Dolphins 1991-1993; Linebacker; Pro-Bowl, 1988
- At least 8 concussions during NFL career.
- Hunting/Fishing guide post NFL
- For the 5 years prior to death at age 45, he experienced worsening memory and cognitive functioning, as well as increasing “short fuse.”
- Died of gunshot to chest while cleaning gun. Not suicide.

Grimsley - Neuropathology

Tom McHale - Died at age 45
A Control???
- Nine-year NFL veteran lineman
- Tampa Bay Buccaneer
- No reported concussions, so wife (and we) thought control
- But as lineman had routine subconcussive blows
- Cornell University graduate, successful restaurateur post NFL, husband and father of three boys
- Died due to drug overdose after a multi-year battle with addiction
Dave Duerson

- Successful businessman post NFL
- ~5 years prior to death, he had worsening short-term memory difficulties
- Increasingly out of control:
  - Short fuse, hot tempered, physically abusive, verbally abusive; lost business, marriage
- Committed suicide Feb 2011, shooting self in chest to avoid hurting brain.
**Not Just Football**

- We have seen CTE in >150 individuals, including mostly football players, but also:
  - Boxers
  - Pro Hockey Players – Enforcers
    - Reggie Fleming
    - Bob Probert
    - Derek Boogaard
  - Other Athletes

**Barry (Tizza) Taylor – Age 77**
Australian Rugby Player
*Competitive Rugby for 19 years*
*235 games for Manly Rugby Union*

**Tizza Taylor – Age 77**
Cognitive Problems in 50’s
Severe Dementia in 60’s

**Not Just Pros**

- Former college football players
- Former college soccer player
Owen Thomas
UPenn Football Co-Captain (Lineman)
Played since age 9; NO Concussions

Suicide at Age 21

Suicide Caused by CTE?

- **Unlikely**
- Suicide is, tragically, too common in this age group
- Complex, multifactorial causes to suicide
- Thomas case showed us:
  - Early evidence of CTE at just 21 years old
  - Another case of CTE with no reported concussions

Neuropathology of CTE is Now Well-Described

- Postmortem description of CTE has had a great impact on public policy and awareness
- However, the public thinks that the science of CTE is far more advanced than it is
CTE: What We Need to Know

• Is CTE Common?
  – We just don’t know!
  – 87 of 91 Pro Football players in BU-VA-CFL Brain Bank have had CTE.
  – Biased!!
  – Mayo study less biased but…
  – Need for longitudinal research with large sample size

CTE: What We Need to Know

• Why do some people get CTE and others do not?
  – all neuropathologically confirmed cases (>150) have had h/o repetitive brain trauma
  – Translation: repetitive brain trauma is a necessary but not sufficient cause of CTE
  – not everyone who hits their head will get it!

CTE: What We Need to Know

• What are the risk factors?
  – Genetics (e.g., APOE, MAPT)
  – Some initial data to suggest that APOE e4 carriers may be at greater risk (Stern et al., Neurology, 2013)
  – Several additional studies currently underway
CTE: What We Need to Know
• What are the risk factors?
  – Genetics (e.g., APOE, MAPT)
  – EXPOSURE Variables
    • Severity and type of trauma; overall duration; total amount of hits; amount of rest/time between hits
    • Age at first exposure to hits
      – To be addressed tomorrow
      – Results of two studies with former NFL players (not generalizable) indicate those who started playing tackle football prior to age 12 had worse cognitive functioning and white matter integrity than those who started playing at age 12 or older….window of neurodevelopmental vulnerability?

Diagnosis of CTE During Life is an Important Next Step
• Differentiate between CTE and other causes of cognitive and behavioral change, including AD, FTLD, PTSD, and persistent/chronic sequelae of previous repetitive or single mTBI
• Understand the true incidence and prevalence of the disease
• Determine the risk factors (including genetic and exposure variables) for CTE
• Begin clinical trials for treatment and prevention

First Step:
*Describe the Clinical Features*

Clinical Features
Three-Four Primary Domains
- Mood: Depression, Hopelessness, Suicidality
- Cognition: Memory & Executive Impairments, Dementia
- Behavior: Impulsivity, Explosivity, Aggression
- Motor: "Post-Traumatic" Parkinsonism, Dysarthria, Ataxia, etc.
Clinical presentation of chronic traumatic encephalopathy

ABSTRACT

Objective: The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neuropathologically confirmed cases.

Methods: Twenty adult male subjects were selected from 31 cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy brain bank. Subjects were all athletes, had no clinical neurodegenerative or motor neuron disease, and had no history of repetitive head impacts.

Results: The behavior/mood and cognitive groups demonstrated symptoms at a significantly younger age than the motor group.

Conclusions: This suggests there are 2 major clinical presentations of CTE, one a behavior/mood variant and the other a cognitive variant. Neurology 2013;81:3-8

Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

Philip H. Montenigro, Christine M. Baugh, Daniel H. Danielvar, Jesse M. M. Andrew E. Budros, Rhoda Au, Douglas I. Katz, Robert C. Cantu, and Robert A. Stern

• Consistent with previous case reports of boxers, we found two different initial clinical presentations:
  – Behavior and/or mood changes
  – Cognitive impairment
• The behavior/mood group demonstrated symptoms at a significantly younger age than the cognitive group.
• Motor features relatively uncommon
Traumatic Encephalopathy Syndrome (TES)  
Montenigro et al., *Alz. Res. Ther.* 2014

• “Traumatic Encephalopathy Syndrome”

• Describes the *clinical presentation* of CTE as well as other possible long-term consequences of repetitive head impacts (e.g., chronic or progressive axonopathy without tauopathy)
  – Behavioral/Mood Variant
  – Cognitive Variant
  – Mixed Variant
  – TES Dementia

Probable and Possible CTE  
*Diagnostic Criteria*

• Probable CTE
  – Meets classification for any TES subtype, Progressive Course
  – Does not meet diagnostic criteria for another disorder more consistently than TES
  – Has a minimum of one positive potential biomarker for CTE

Similar to Alzheimer’s Disease, Biomarkers, in Addition to Clinical Evaluation, will Lead to Accurate *in vivo* diagnosis
Stay tuned for Dr. Mac Donald

Step Three: Develop the Best Acronym Ever!
“Chronic Traumatic Encephalopathy: Clinical Presentation and Biomarkers”

Goal:
To Develop Biomarkers to Diagnose CTE During Life

Principal Investigator: R.A. Stern
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National Institute of Neurologic Diseases and Stroke
National Institute of Aging
National Institute of Childhood Health and Development

DETECT Study - Subjects
- ~100 former NFL players
  - ages 40-69
  - positions with highest exposure to RBT
  - currently symptomatic
- 30+ controls
  - same age
  - no brain trauma exposure

DETECT Study - Measures
- Neuroimaging (MRI, DTI, SWI, fMRI, MRS, etc.)
  - Shenton, Koerte, and Lin (BWH, Harvard)
- Lumbar Puncture (CSF Tau, beta amyloid, monoamines)
  - Trojanowski and Shaw (Penn); Mann (Columbia)
- EEG (BrainScope)
  - Prichep (NYU)
- Genetics (APOE, MAPT, MAOA-u)
- Clinical Exams (Neuro, Cognitive, Psych, Motor)
- When we started, there were no measures of blood tau or brain tau on the horizon
Last DETECT Subject
October 2015

- Preliminary published and unpublished findings to date

Cavum Septum Pellucidum (CSP)
- CSP is common in individuals with neuropathologically-confirmed CTE, with increasing frequency of CSP in worse neuropathological stages (McKee et al., 2013, *Brain*)

MRI Measures of Cavum Septi Pellucidi (CSP)
Koerte et al., 2015, *J Neurotrauma* (M. Shenton, PNL, BWH)
- 72 former NFL and 14 controls from DETECT
- Former NFL group had a higher rate of CSP, a greater length of CSP, and a greater ratio of CSP length to septum length.
- Additionally, in the NFL group, a greater length of CSP was significantly associated with decreased performance on a list learning task.

Magnetic Resonance Spectroscopy
A “Virtual Biopsy”
Magnetic Resonance Spectroscopy (MRS) (Dr. Alex Lin et al., BWH)
- NFL-Control differences in brain chemistry both in metabolite concentration and brain region.
  - In the posterior cingulate gray matter, glutathione (GSH) was significantly reduced (p<0.05), reflective of neuroinflammation
  - In parietal WM, glutamate (Glu) and myo-inositol (mI) were significantly increased (p<0.05), possibly reflecting glial activation
- New DoD Grant just funded to examine glial activation in CTE and AD

The Next Important Step
Brain Tau Imaging
- Over the past three years, 4+ groups around the world have developed new PET scan ligands which bind to abnormal tau and which do not appear to attach to other proteins
- These have now been used successfully in humans, though are in the early phases of development

The Next Important Step
Brain Tau Imaging
Early Clinical PET Imaging Results with the Novel PHF-Tau Radioligand [F-18]-T807

DETECT PET Study
Sponsored by Avid Radiopharmaceuticals
- T807 (AV 1451) PET Tau Imaging and Florbetapir PET Amyloid Imaging added to DETECT protocol.
- (VERY) Preliminary Findings
Comparison of AV1451 and CTE Unique Neuropathology

Hypothesized Differences in PET Ligands between CTE, Alzheimer’s Disease Dementia, and Controls

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<tr>
<th></th>
<th>CTE</th>
<th>AD</th>
<th>CNTL</th>
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<tbody>
<tr>
<td>Tau Ligand, [18F]-T807</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Aβ Ligand, [18F]-florbetapir</td>
<td>-</td>
<td>+</td>
<td>-</td>
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DoD Grant Now Underway
DoD W81XWH-13-2-0064
Traumatic Brain Injury Research Award
“Tau Imaging of Chronic Traumatic Encephalopathy”
Pi’s: Shenton and Stern
Fluid Biomarkers

• CSF
• Blood

DETECT – Cerebrospinal Fluid
Preliminary Findings

• Former NFL group has significantly greater p-tau to total tau ratio than Control group

<table>
<thead>
<tr>
<th>Analyte</th>
<th>CTL Mean (SD)</th>
<th>NFL Mean (SD)</th>
<th>Stat (adjusted for BMI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Tau</td>
<td>49.2 (3.6)</td>
<td>38.7 (2.2)</td>
<td>3.39</td>
<td>0.0664</td>
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<tr>
<td>p-Tau</td>
<td>16.9 (1.5)</td>
<td>19.5 (0.9)</td>
<td>3.44</td>
<td>0.0647</td>
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<tr>
<td>p-tau/t-tau</td>
<td>0.35 (0.04)</td>
<td>0.50 (0.04)</td>
<td>6.39</td>
<td>0.0120</td>
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A Blood Test???

Blood Based Biomarkers?

• Plasma Tau (Quanterix Simoa Platform)
  – Promising preliminary results: plasma tau significantly correlated with CSF tau
  – But what does it mean to measure tau that is in the blood and not from the brain??
• Plasma exosomal tau – measuring tau from brain cells through a blood test
**Exosomes**

- Exosomes are cell-derived nanovesicles present in biological fluids, including blood, saliva, cerebrospinal fluid, and urine.
- Mirror the features of the parent cell, including the cargo proteins.
- Examined in oncology since the 1970’s (Tumor-Secreted Exosomes).
- Exosomes are very stable and make a “liquid” biopsy possible.
- And... they cross the blood-brain barrier (BBB)!

**Generation of Neuronal Exosomes**

**Exosome Crosses BBB**

**Isolate Brain-Derived Exosomes from Plasma**
Plasma Exosomal Tau

- 78 former NFL and 16 controls from DETECT
- Extracellular vesicles isolated from plasma using size exclusion chromatography
- Fluorescent nanoparticle tracking analysis used to determine the number of vesicles staining positive for tau

NFL group had higher exosomal tau than the control group (p < .0001)

Exosomal tau discriminated between the groups
- 82% sensitivity
- 100% specificity

Within the NFL group, higher exosomal tau associated with worse memory (p = 0.0126) and psychomotor speed (p = 0.0093)

Only the beginning! Many limitations and need for refinement, replication, and post-mortem validation

Future Research

Risk Factors
- Repetitive Head Impact Exposure
  - Sport
  - Rotation
  - Age of First Exposure
  - Total Duration
  - Frequency and Type of Hits
  - Severity of Hits
- Genetics
  - ApoE
  - MAPT
  - Others

Diagnosis During Life
- Clinical Features and Diagnostic Criteria
- Traumatic Encephalopathy Syndrome (TES)
- Reversible/Probable CTE
- Neuroimaging Biomarkers
  - MRI, DTI, MRS, PET
- CSF and Blood Biomarkers
  - Exosomal Tau
  - Plasma Tau
- Differential Diagnosis
  - Alzheimer’s disease
  - FTLD
  - Depression, etc.
Large, Multi-Center, 7-Year NIH U01 Grant Just Funded

Principal Investigators
Robert A. Stern, Ph.D. (Contact PI)
Jeffrey Cummings, M.D.
Eric Reiman, M.D.
Martha Shenton, Ph.D.

High Exposure Group
120 Former NFL Players
Asymptomatic, Symptomatic, Dementia

Medium Exposure Group
60 Former College Players
Asymptomatic, Symptomatic, Dementia

Control Group
60 No-Contact Sport/no-TBI Controls
All Asymptomatic

Biomarkers
Fluid: CSF & Blood
Neuroimaging: MRI, DTI, fMRI, MRS, PET-
amyloid, & PET-tau

Clinical Diagnosis
Traumatic Encephalopathy Syndrome
Behavior/Mood, Cognitive, Mixed, Dementia Subtypes & Chronic Traumatic Encephalopathy Probable, Possible, Unlikely

Clinical Exams
Neurocognitive, Mood, Behavior, & Motor Tests

Exposure
Baseline
3 Yr Follow-up

Risk Assessment:
Head Impact Exposure & Genetic Polymorphisms

Disease Course:
Clinical and Biomarker Characteristics

Consensus Statement on Diagnostic Criteria

Future Research
- Once we can diagnose CTE during life, we will be able to begin clinical trials for treatment
- And, if we can detect it early in the disease course, prior to symptoms, we can conduct clinical trials for prevention!

BU CTE Clinical Research Funding
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NFL Players Association – Travel for study participants
JetBlue – Travel for study participants
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• Boston VAMC
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