Chronic Traumatic Encephalopathy 2011: What we’ve learned from athletes

Ann C. McKee M.D.
Professor of Neurology and Pathology
Boston University School of Medicine
Director, Neuropathology, New England Veterans Healthcare System and Brain Banks
Over the past 3.5 years, the brains and spinal cords of over 100 athletes and military veterans who experienced mTBI have been donated to the VA MTBI Brain Bank.
The relationship between concussion and CTE

• Concussion, subconcussion and post-concussion syndrome - temporary states of neuronal and axonal derangement

• CTE - a progressive neurodegeneration that is triggered by repetitive mTBI, including concussion and subconcussive blows, but evolves slowly over decades. Symptoms are not usually apparent until many years later.

• Repetitive neuronal and axonal disturbance superimposed on unresolved injury - initiates a series of metabolic, ionic, membrane, and cytoskeletal disturbances that trigger the pathological cascade that leads to CTE.
Chronic Traumatic Encephalopathy
or Dementia Pugilistica

First reported by Martland in 1928 in Boxers *Punch drunk. JAMA* 91:1103–1107, 1928

Martland described the spectrum of abnormalities found in

“nearly one half of the fighters who have stayed in the game long enough”

In 2009, in the worlds literature: 51 cases of CTE including 3 cases from BU

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy following Repetitive Head Injury.
*McKee et al. J Neuropath Exp Neurol, 2009 68(7): 709-735*
Pathology of CTE

Brain Atrophy

Abnormal tau protein

TDP-43

Normal

CTE

Neurofibrillary tangles

Inclusions and neurites
Framingham Heart Study

Half-brain sections
Immunostained for hyperphosphorylated tau protein

61 year old man
68 year old man

>150 subjects; >70 cognitively intact
Longitudinally assessed since 1948
Hyperphosphorylated tau protein

Normal Control  CTE

amygdala  frontal cortex
Hyperphosphorylated tau protein

Normal Control  CTE

frontal cortex  hippocampus
**Unique Pathology of CTE**

Hyperphosphorylated tau protein as Neuronal and Glial tangles

Unlike any other tauopathy

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<tr>
<th>perivascular</th>
<th>superficial layers</th>
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*depths of the sulcus*

*glial tangles*
Pathologically CTE is entirely distinct from AD

Normal
No Tau, no Aβ

CTE
Tau, no Aβ

Alzheimer’s disease
Tau and Aβ
John Grimsley

• Linebacker, 9 years in NFL
  Houston Oilers 1984-1990
  Miami Dolphins 1991-1993

• Pro-Bowl, 1988

• Married, father of 2 sons

• Retired from football at the age of 32

• Age 40: problems with short-term memory, attention, concentration, judgment, and ability to multitask.

• Age 45: death from accidental self-inflicted gunshot wound

Celebrating the Life of John Grimsley

Dave Duerson

Death at age 50 years

Began playing football at age 8
   24 total seasons, safety in college and pro
> 10 concussions
11-year NFL career
   Several concussions with loss of consciousness
   Never admitted to hospital
No known brain trauma since retiring from

Post-NFL, very successful in food supply industry (Duerson Foods)

Very active in NFLPA; Benefits Board

General health: very good

Work and financial difficulties began in 2007

No history of depression or other psychiatric difficulties; no substance abuse
• Long-standing complaints of headaches since NFL and onward.

• Over the ~5 years prior to death, he had worsening short-term memory difficulties, as well as problems with language and “vision”

• Increasingly out of control:
  Short fuse
  Hot tempered
  Physically abusive
  Verbally abusive
Owen Thomas
UPenn Football Player

Suicide at age 21. Recent stress and academic decline.
Wally Hilgenberg

Death at age 66 years

- Linebacker 16 years Minnesota Vikings
  >10 concussions, multiple cervical spine injuries
- Age 56: Slow and steady cognitive decline
- Difficulty understanding things at a “deeper level”
- Worsening planning and organization skills
- Memory loss
- Apathy
- Age 64: Weakness and muscle atrophy, fasciculations, spasticity Dx: ALS
- Death: age 66
CTEM

TDP-43

TAU
3 athletes with CTE (now 6) also had a progressive motor neuron disease with TDP+ inclusions in motor neurons of brain and cord (CTEM).

These findings indicate that in some individuals who experience repetitive mTBI may develop a motor neuron disease.

Retrospective case-control cohort study found that playing in the NFL between 1960 and 2010 was associated with a RR of 2.25 for being clinically diagnosed with ALS compared to age and gender matched controls.
Chronic traumatic encephalopathy (CTE)

So what do we know?

- CTE is a progressive neurodegenerative disease distinct from Alzheimer’s disease, that we are finding in the brains of many professional football players, boxers, veterans and hockey players.

- CTE is a tauopathy and TDP-43 proteinopathy associated with repeated mTBI that most commonly occurs in an individual’s teens and early twenties.

- Once triggered, the neurodegeneration progresses slowly over decades to involve widespread degeneration of many brain structures.

- The symptoms of CTE are often insidious and begin in mid-life with prominent early personality and behavioral changes (short fuse, depression, suicidal ideations, impulsivity) and memory loss. There is a slow deterioration that progresses to include dementia, parkinsonism, gait and speech disorders.
Chronic traumatic encephalomyelopathy (CTEM)

So what do we know?

- A subset of individuals who develop CTE, approximately 10%, also develop a motor neuron disease, CTEM

- CTEM is characterized by widespread TDP-43 deposition in the frontal cortex, especially motor cortex, the subcortical white matter, basal ganglia, diencephalon, brainstem and spinal cord.

- Individuals with CTEM tend to die at earlier stages of disease than individuals with CTE, as a result, their cognitive and behavioral symptoms also tend to be less severe
CTE/CTEM

What do we need to know?

- We do not understand what triggers CTE in some individuals
- We cannot diagnose it during life
- We cannot treat it
- Preventative education and increased awareness concerning management of mTBI in sports and military will decrease the frequency of CTE
- We need to understand the basic mechanisms of CTE pathobiology in order to treat it effectively
- Current work includes reproducing the injury in experimental model systems and beginning preclinical therapeutic trials
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CTE: it affects our service members, our athletes and our kids

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