Traumatic Encephalopathy in Athletes

Progressive tauopathy following repetitive head injury
Center for the Study of Traumatic Encephalopathy

September 2008 SLI and BU founded the first ever research center dedicated to CTE

A Collaboration Between Sports Legacy Institute and Boston University School of Medicine

Goals

1. Establish a Brain Donation Registry
   Current or retired athletes, with and without history of concussion, to agree to donate brain tissue following death.

2. Conduct Clinical Research
   Examinations of retired athletes, including cognitive, mood, and neurological assessments, as well as brain MRI and spinal taps (to measure proteins in cerebrospinal fluid). Study longitudinally and examine brains following death.

3. Expand the Brain Bank
   Brain tissue repository for the examination of the underlying neuropathology associated with repetitive concussion in athletes.
Center for the Study of Traumatic Encephalopathy

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Former Harvard Football Player and Prof Wrestler

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Co-Director Boston University Alzheimer’s Disease Center  
Associate Professor of Neurology  
Boston University School of Medicine
The CSTE Brain Bank Registry

- Living athletes are lining up to be part of this groundbreaking research

<table>
<thead>
<tr>
<th>National Football League (41)</th>
<th>National Hockey League (5)</th>
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* As of Sept 2009
3 active NFL players promise their brains for concussion research. 'The culture has to change'

Sean Morey
Arizona Cardinals

Lofa Tatupu
Seattle Seahawks

Matt Birk
Minnesota Vikings
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What is Chronic Traumatic Encephalopathy?
also known as Dementia Pugilistica
What is Chronic Traumatic Encephalopathy? also known as Dementia Pugilistica

• CTE is a slowly progressive neurodegeneration that occurs after repetitive mild traumatic brain injury

• It was first described in boxers in 1928 (Martland, JAMA).

• There are 52 cases of neuropathologically verified CTE in the world's literature (including 3 from BU)
Chronic Traumatic Encephalopathy

Of the 52 neuropathologically confirmed cases of CTE, 47 (90%) occurred in athletes:

- 41 boxers (2 from BU) (76%)
- 5 football players (1 from BU) (10%)
- 1 professional wrestler (2%)
- 1 soccer player (2%)

10% non-athletes

- 1 physical abuse (2%)
- 2 head banging behavior (4%)
- 1 circus clown (2%)
- 1 epilepsy (2%)
First symptoms of CTE are insidious

CTE commonly begins as a personality change, behavioral and mood disturbance in midlife

- First symptoms of CTE age 25-76 years; m = 43 yrs

- Long latent period between stopping the sport and onset of symptoms:
  Only 1/3 are symptomatic at time of retirement from sport
  mean onset of symptoms = 8 years after stopping (range: 0-37 yrs)
Chronic Traumatic Encephalopathy

Long latent period

- Athletes began their sport at young ages: 11-20 yrs; mean 16
- Played for varying lengths of time: 14-23 yrs; mean 18

Much longer, slower course than most dementing conditions such as Alzheimer’s disease

- Interval between onset of symptoms and death: 2-46 yrs, mean 18
- Age at death: 23-91 yrs, mean 55
Symptoms of CTE

- **Cognitive changes:** 69%
  - Memory loss
  - Dementia
- **Personality/Behavioral changes:** 65%
  - Aggressive or violent behavior
  - Confusion
  - Mood changes, usually depression
  - Paranoia
  - Irritability
- **Movement abnormalities:** 41%
  - Gait problems
  - Parkinsonism
  - Speech abnormalities
CTE in boxers

• Boxing is the most frequent sport associated with CTE
• Boxers age at death: 23-91 years; \( m = 60 \) years
• Disease duration is the longest in boxers, with case reports of individuals living for 33, 34, 38, 41, and 46 years with smoldering, yet symptomatic, disease.
• Boxers with long-standing CTE are frequently demented (46%) and may be misdiagnosed clinically as Alzheimer’s disease
CTE in Football players (11)

5 reported in literature (1 from BU); our 6 additional cases

- 8 died suddenly in middle age (8/11 = 73%):
  (age at death, 36-80 years; m = 45 years)
- 7 of the 11 deaths were associated with erratic behaviors (64%):
  3 from suicide
  2 substance abuse
  1 during a high-speed police chase
  1 accidental gunshot while cleaning his gun
Common symptoms in football players

- mood disorder (mainly depression)
- memory loss
- 80%: paranoia
  - poor insight or judgment
- outbursts of anger or aggression
- 60%: irritability
  - apathy
- confusion
- 40%: reduced concentration
  - agitation
  - hyperreligiosity
### Football players with CTE

<table>
<thead>
<tr>
<th>#</th>
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<th>Years stopping sport - death</th>
<th>College FB years</th>
<th>NFL FB years</th>
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<td>4</td>
<td>0</td>
<td>8</td>
<td>wide receiver</td>
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How do you recognize CTE at autopsy?

What are the key pathological features?
Pathology of CTE

**Gross:** 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 II and III ventricles
- Cavum septum pellucidum with fenestrations

- Pallor of the substantia nigra
Normal gross appearance

3 years of professional football. Cognitively intact.
Death at age 49.

Brain weight: 1580 grams
16 years of professional football

Death at age 66 years with apathy, MCI

Brain weight: 1560 grams
16 years of professional football

Death at age 66 years with apathy, MCI

enlarged ventricles
16 years of professional football

Death at age 66 years with apathy, MCI

enlarged ventricles
cavum septum pellucidum
Fenestrated septum pellucidum
Fenestrated septum pellucidum

Enlargement of III ventricle

Fenestrated septum pellucidum
Frontal Contusions
10 years of professional football

Death in his 80s with dementia

Brain weight: 1450 gms
10 years of professional football
Death in his 80s with dementia

Severe II and III ventricular dilatation

Brain weight: 1450 gms
10 years of professional football

Death in his 80s with dementia

Cavum septum pellucidum
10 years of professional football

Death in his 80s with dementia

Marked medial temporal atrophy
10 years of professional football

Death in his 80s with dementia

severely fenestrated septum pellucidum posteriorly
10 years of professional football

Death in his 80s with dementia

Dilation of IIIrd ventricle
Shrinkage of the mammillary bodies
thinning of the hypothalamic floor

CTE brain

normal brain
pallor of the substantia nigra
Microscopic Pathology of CTE

Neurofibrillary degeneration

Extensive tau-immunoreactive NFTs, glial tangles, and neurites throughout the brain

Widespread distribution:
- Cerebral cortex – frontal and temporal lobes
- Medial temporal lobe – amygdala, hippocampus, entorhinal cortex
- Subcortical white matter
- Thalamus, hypothalamus, mammillary bodies
- Brainstem
- Spinal cord

Unique pattern of involvement:
- Superficial
- Perivascular
- Patchy, irregular, depths of the sulcus
- Glial tangles
CTE: Tau immunoreactive NFTs

Cerebral cortex – primarily the frontal and temporal lobes

Medial temporal lobe – amygdala, hippocampus, entorhinal cortex
CTE: Tau immunoreactive NFTs
Subcortical Nuclei

Hypothalamus
Mammillary bodies

Thalamus
CTE: Tau immunoreactive NFTs

Brainstem and Spinal cord

Substantia Nigra  Locus ceruleus

Midbrain  Pons  Medulla  Cord
CTE: Neurofibrillary degeneration
prominent perivascular distribution
greatest at sulcal depths
CTE: Neurofibrillary degeneration
Prominent glial tangles
World Champion Boxer

dead at age 73 years, profoundly demented

No Aβ

Tau immunohistochemistry
Professional Boxer

death at age 80 years, severely demented

Tau immunohistochemistry

Aβ: moderate diffuse plaques
sparse neuritic plaques
Boxers

Death in long term care facility after long battle with dementia
Football player: 10 years in NFL
death at age 45 years: memory loss, confusion, executive dysfunction

No Aβ

Tau immunohistochemistry
Frontal cortex

65 y.o. control  45 y.o. NFL football  80 y.o. prof boxer

Tau immunohistochemistry
Amygdala

65 y.o. control

45 y.o. NFL football

73 y.o. prof boxer

Tau immunohistochemistry
Football player: 16 years in NFL
death at age 66 years: memory loss, confusion, executive dysfunction, profound apathy

Tau immunostaining
No Aβ
Football player: 16 years in NFL
dearth at age 66 years: memory loss, confusion, executive
dysfunction, profound apathy
Football player: 9 years in NFL
death at age 45 years: depression, poor decision making, substance abuse

Orbital frontal  Hippocampus  Temporal  Amygdala

Aβ: rare diffuse plaques
Football player: 10 years in NFL

Death in his 80s: dementia

Aß: extremely rare diffuse plaques
Football player: 3 years in USFL, NFL
Death at age 49. Cognitively intact

Aβ: rare diffuse plaques
College football player

Death at age 42. Confusion, depression, erratic behavior, substance abuse

No Aβ
High school football player
Death at age 18. Cognitively intact. Focal evidence of perivascular tau

No Aβ

Tau immunohistochemistry
High school football player
Death at age 18. Cognitively intact. Focal evidence of perivascular tau

No Aβ
CTE: Unique, predictable pattern of tau neurofibrillary change very distinct from Alzheimer’s disease or any other tauopathy.
Preliminary evidence for the severity of tau immunoreactivity and:

1. The duration of exposure, i.e. number of playing years
2. The length of survival after exposure

Football players

- 16 NFL years
- 10 NFL years
- 3 NFL/USFL years

66 years
45 years
49 years
Normal Controls

Longitudinally assessed since 1948

Immunostained for AT8 tau

68 year old man
Beta amyloid deposition

CTE:
none in most cases
modest when found

AD:
universal feature
severe deposition
I
II
III
IV
V
VI
WM
CONTROL
CTE
CTE
Alzheimer’s
Aβ
CTE is entirely distinct from Alzheimer’s disease

Normal

CTE

Alzheimer’s disease

no Aβ, no tau

tau
no Aβ

tau and Aβ
Summary

- The evidence suggests that CTE is associated with repeated sublethal brain trauma that most commonly occurs in an individual’s teens and early twenties.

- There is characteristically a long latent period (mean = 8 years, range 0-37 years) between stopping play of the sport and the onset of symptoms.

- Once triggered, the neurodegeneration progresses slowly, with an mean survival of 18 years after the onset of symptoms (range 2-46 years).
Chronic Traumatic Encephalopathy

• The symptoms of CTE are often insidious and begin in mid-life with prominent early personality and behavioral changes and memory loss.

• There is a slow deterioration that progresses to include dementia, Parkinsonism, gait and speech disorders.

• In the advanced cases, the dementia make be clinically misdiagnosed as AD or FTD

• The severity of the cortical and medial temporal lobe degeneration appears to increase with exposure, i.e. playing time, and survival after the injury
Chronic Traumatic Encephalopathy in football players

- 73% of football players with CTE have died suddenly in middle age (age at death, 36-80 years; m = 45 years)

- 64% experienced tragic deaths from suicide, substance abuse or erratic dangerous behavior

- To date, all of the brains from football players that we have studied have shown at least focal evidence of CTE
Chronic Traumatic Encephalopathy

- Although CTE is most commonly found in athletes, many individuals are susceptible: epileptics, persons who suffer falls, accidental blows from moving objects, or motor vehicle accidents, and military veterans.
Acknowledgments

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