Recurrent Sports-Related Traumatic Brain Injury and Tauopathy

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Dementia Pugilistica

First described in boxers by Martland in 1928


Corsellis (1973) first described the neuropathological changes in the brains of boxers
Chronic Traumatic Encephalopathy (CTE) = Dementia Pugilistica

- Progressive neurodegenerative disease, similar to Alzheimer’s disease but is a unique disease!
- Believed to be caused by repeated trauma to brain, including mild concussions and subconcussive blows.
- Not prolonged post-concussion syndrome.
- Symptoms begin years or decades after the head trauma and continue to worsen.
Chronic Traumatic Encephalopathy (CTE) = Dementia Pugilistica

continued

• Early Symptoms:
  – memory and cognitive difficulties
  – depression
  – impulse control problems and behavior change
  – Later on: movement abnormalities (including Parkinsonism)

• Eventually leads to full-blown dementia
• The only fully preventable cause of dementia
Neuropathology
Chronic Traumatic Encephalopathy (CTE)

- At the time of publication, there were 52 cases of neuropathologically verified CTE in the world’s literature (including 3 from BU).
- We have now examined over 35 cases (well over half of the known cases).
CTE: Microscopic Pathology

• Neurofibrillary degeneration
• Extensive tau-immunoreactive neurofibrillary tangles, 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
CTE: Tau NFTs
Brown = stained for Tau
Normal brain should have no brown

Frontal cortex
Insular cortex
Temporal cortex
Medial temporal lobe
Football player: 16 years in NFL

death at age 66 years: memory loss, confusion, executive dysfunction, profound apathy

No Aβ
Alzheimer’s versus CTE

• Both are progressive, incurable, neurodegenerative diseases.
• Early symptoms
  – AD 60’s
  – CTE 20s-50s
• Both are currently only diagnosed through post-mortem examination of brain tissue.
• CTE = tau (neurofibrillary tangles)
• AD = tau AND beta amyloid plaques
Beta amyloid deposition

CTE: none in most cases, modest when found

AD: universal feature, severe deposition
CTE in Pro Sports other than Boxing
First Five Cases Prior to BU CSTE (Omalu et al.)

- Mike Webster; 50 yrs; died from MI depression, cognitive problems, homeless, unemployed (died 2002)
- Terry Long; 45 yrs; Suicide (died 2005)
- Andre Waters; 44 yrs; Suicide (died 2007)
- Justin Strzelczyk; 36 yrs; “Downward spiral; depression, behavioral changes; Police chase; drove truck into tractor trailer (died 2004)
- Chris Benoit; 40 yrs; Suicide and murder of wife and child (died 2007)
First BU CSTE NFL Case
John Grimsley
Died at Age 45

• Houston Oilers 1984-1990; Miami Dolphins 1991-1993; Linebacker; Pro-Bowl, 1988
• No history of performance-enhancing drugs
• At least 8 concussions during NFL career
• Died of gunshot wound to chest while cleaning gun. No evidence of suicide.
• For the 5 years prior to death at age 45, he experienced worsening memory and cognitive functioning, as well as increasing “short fuse.”
Grimsley - Neuropathology

65 yr old healthy control

Grimsley 45 yr old CTE

73 yr old boxer with dementia and CTE
Tom McHale
Died at age 45

- Nine-year NFL veteran lineman
- Tampa Bay Buccaneer
- Cornell University graduate, former restaurateur, husband and father of three boys
- 2-3 possible concussions, but as lineman had routine blows
- Died due to drug overdose after a multi-year battle with addiction.
First Member of HoF and NFL’s 88 Plan
Lou Creekmur
Died at age 82

• Former offensive lineman for the Detroit Lions and eight-time Pro Bowler. Member of Hall of Fame.
• Ten seasons for the Lions; famous for suffering at least thirteen broken noses while playing without a facemask.
• Died from complications of dementia while in a nursing home after a thirty year decline: cognitive and behavioral issues, memory loss, problems with attention and organization, angry and aggressive outbursts. Wife referred to him as “punchy” for last 30 years.
Creekmur - Neuropathology
Not Just Pros!
First College Football Case
Mike Borich
Died at age 42

- Snow College and Western Illinois University player in the 1980s
- Known to have approximately 10 concussions during his college football career with no subsequent concussions or head injuries since that time.
- Division I college football coach, named Offensive Coordinator of the Year in 2001, while coaching at Brigham Young University; coached for the NFL’s Chicago Bears in 1999-2000.
- Left coaching in 2003 struggling with overwhelming drug and alcohol addictions, ultimately dying from a drug overdose in February 2009.
Not Just Football!
First Pro Hockey Player
Reggie Fleming
Died at age 73

• Defensemen and forward for six NHL teams from 1959 to 1971.
• His 13 seasons and 749 NHL games were part of a storied professional career that lasted over twenty years.
• Remembered today for his hard-nosed play and combative style that led to 108 NHL goals, 1468 penalty minutes, and a Stanley Cup with the 1961 Chicago Blackhawks.
Fleming – History

• Sx of CTE for decades; Dx’d with “manic depression” in his early 40’s, due to frequent extreme behavioral outbursts.
• Described as “out of control,” with significant problems controlling his eating, drinking, gambling, and temper.
• Significant attention, concentration, memory, executive impairment.
• Full dementia in his final two years.
Fleming - Neuropathology
Not Just Adults!
Youngest Evidence of CTE: Death at age 18 HS Athlete
A Second Abnormal Protein Now Found in CTE: TDP-43

- Abnormal protein TDP-43 has been found in 85% of CTE positive cases.
- TDP-43 is associated with other neurodegenerative diseases like FTD, but in CTE it is in a unique pattern.
- More research underway.

Frontal cortex

Substantia Nigra
Is CTE Common?

• All 13 of 13 football players examined by the BU CSTE have had CTE.
• What is the denominator? What if next 87 football players’ brains were “clean”?
• Need for longitudinal research with large sample size.
CSTE Brain Donation Registry

• Began approximately 12 months ago.
• Current size = ~350
• 750 Total
• All participants undergo annual telephone interview regarding cognitive and behavioral symptoms, brief cognitive assessment, as well as athletic, concussion, and medical history.
• We are beginning a new registry for combat veterans.
Pilot Imaging Data on 6 Retired Pro Athletes

- Brigham and Women’s Hospital
- Structural MRI with 3D
- DTI with Tractography
- MRS
Saggital view of the brain with 3D reconstruction of the cortex showing the right hemisphere. The athlete (left panel) is in gold and the healthy volunteer (right panel) in blue. Note the atrophy in the frontal and parietal lobe regions, as well as in the area of the Sylvian fissure in the athlete compared to the healthy volunteer.
Coronal view of the brain. The red arrows point to the amygdala-hippocampal complex where in the athlete there is an increase in CSF (black region) compared with the healthy volunteer. Yellow arrows point to cortical atrophy that is visible in the frontal lobe as well as in the area of the Sylvian fissure.
Athlete Left Panels

Age-matched control

Right Panels

Diminished Corpus Collosum and Fiber Bundles
Above: MRI with MRS voxel locations of posterior cingulate gyrus (PCG), anterior cingulate gyrus (ACG), parietal white matter (PWM), and anterior white matter (AWM).

Right: Representative spectra showing control (in red) and athlete (in blue) for each region of the brain. Spectra were normalized to Cr so that they could be compared. Arrows indicate increased or decreased metabolite signal for each metabolite. Major peaks are labeled as N-acetyl aspartate (NAA), Glutamate/Glutamine (Glx), Creatine (Cr), Choline (Cho), and myo-inositol (mI).
Repetitive Subconcussive Trauma

- Concussions are just the tip of the iceberg
- Reminder: Long-term progressive tauopathy (CTE) is caused by repetitive blows to the head, including mild, non-symptomatic, subconcussive trauma
What We Still Need to Learn

• How common is CTE in athletes (at all levels)?
• Is CTE found in combat veterans?
• What are the risk factors of CTE?
  o Genetic
  o Type of trauma (LOC, grade of concussion, subconcussive blow)
  o Impact of Blast injuries (single, repetitive)
  o Frequency and time interval between successive head traumas
  o In athletes: Positions and sports (i.e., “load” of trauma?)
  o Age of individual at time of injury(ies) and duration of exposure
What We Still Need to Know

continued

• How can we detect and diagnose CTE prior to death?
• What treatments and prevention strategies will be effective?
• Is CTE triggered by repetitive blast injury in a similar fashion to repetitive (sub)concussive trauma?
• diffuse axonal injury?
• microhemorrhages?
Implications for Understanding of Blast Injury in Military Settings

• Long-term consequences of repetitive blast injuries are currently unknown.

• In athletes, the clinical symptoms of CTE begin years or decades following trauma.
  – Will there be a growing epidemic of progressive dementia in veterans?

• Symptoms of CTE can mimic PTSD.

• Many members of the military may have also had previous and/or concurrent contact sport involvement.
Blast Injury (continued)

• How can risk be reduced?
  – Limit repetition (“return to play” rules)
  – Changes to helmets to absorb the wave, akin to new football helmets absorbing force
  – Who is at increased risk?
  – In-theatre acute “treatment”
Future Research:
Animal Modeling of CTE & Development of Protective Headgear
Boston University Center for the Study of Traumatic Encephalopathy

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And all the athletes, living and deceased, who have participated in our research

...and all the future athletes...