Disclosures

• I have no relevant financial relationships to disclose
Learning Objectives

• Identify the key features of the pathognomonic lesion of CTE

• Distinguish CTE from other age-related tauopathies

• List common co-morbidities of CTE
Paul Pender (1930-2003)
First case of CTE at VA/Boston University

World Champion Boxer
Marine
Severe Dementia
Clinical diagnosis: AD

SEVERE TAUOPATHY with no Aβ

McKee et al. J Neuropath Exp Neurol, 2009 68(7): 709-735
Chronic Traumatic Encephalopathy (CTE)

Punch drunk Martland JAMA 91:1103–1107, 1928

Chronic Traumatic Encephalopathy Critchley In: Homage a Clovis Vincent, Paris, Malonie, 1949

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy following Repetitive Head Injury
McKee et al. J Neuropath Exp Neurol, 2009 68(7): 709-735
45 year old ex-NFL players

Tom McHale

Lineman, 9 years NFL
Retired from NFL at age 32
Age 40: business failed, painkillers, short-term memory problems, depression, irritability
Age 45: death from overdose

John Grimsley

Linebacker, 9 years in NFL
Retired from NFL at age 32
Age 40: short term memory problems, attention and concentration difficulties, poor judgment
Age 45: death from accidental GSW
VA-BU-CLF Brain Bank, 2008-present

To investigate the long-term consequences of TBI

>1250 brain donors
Brain donations to the UNITE Brain Bank per year

N = 1025
Brain donations to the UNITE (VA-BU-CLF) Brain Bank by primary exposure source

- Football: 708
- Ice Hockey: 45
- Wrestling: 22
- Combat Sports (Boxing, MMA): 40
- Military: 147
- Other: 116
Brain donations from American football players to the UNITE (VA-BU-CLF) Brain Bank

N = 708
1928
Martland describes the clinical syndrome of “punch drunk” in boxers

1949
Critchley introduces the term “chronic traumatic encephalopathy”

1973
Corsellis et al describe the clinicopathological features in 15 boxers

2005, 2006
Omalu et al describe CTE in 2 NFL players

2009
McKee et al review 19 CTE cases in literature; 3 new cases, new clinicopathological findings/ptau immuno

2009
McKee et al criteria for pathological diagnosis of CTE and a staging scheme

2013
McKee et al criteria for pathological diagnosis of CTE and a staging scheme

2015
1st NINDS consensus criteria, consensus pathological pathognomonic lesion

2019
McKee et al criteria for pathological diagnosis of CTE and a staging scheme

2019
Mez, Daneshvar et al. DOSE-response between years of football and CTE

2017
Mez, Daneshvar et al. JAMA CPC study of 202 football players, 99% NFL players with CTE

2020
Quantitative validation of McKee staging scheme

Timeline of CTE

Publications
What is CTE?

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHI), including symptomatic concussions and asymptomatic subconcussive injuries, often incurred during contact sports.

CTE has been neuropathologically diagnosed in American football, rugby, ice hockey, soccer players, boxers, wrestlers, and individuals exposed to domestic violence, head banging, and blast injuries.

CTE can only be diagnosed after death by post-mortem examination. It cannot be diagnosed with certainty during life.
CTE LESION

depth of the sulcus

ptau

vessels
1. Perivascular p-tau lesion (CTE lesion)
Diagnostic features of CTE:

2. CTE lesions are found at the sulcal depths
### Stages of Tau Pathology

<table>
<thead>
<tr>
<th>Stage</th>
<th>Images</th>
<th>Age at Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td><img src="image1.png" alt="Image" /></td>
<td>m age: 28.3 ± 13 yrs</td>
</tr>
<tr>
<td>Stage II</td>
<td><img src="image2.png" alt="Image" /></td>
<td>m age: 44.3 ± 16 yrs</td>
</tr>
<tr>
<td>Stage III</td>
<td><img src="image3.png" alt="Image" /></td>
<td>m age: 56.0 ± 14 yrs</td>
</tr>
<tr>
<td>Stage IV</td>
<td><img src="image4.png" alt="Image" /></td>
<td>m age: 77.4 ± 12 yrs</td>
</tr>
</tbody>
</table>

CTE stage significantly correlates with age at death and total number of years playing football. 

McKee et al, 2013, Brain
Pathognomonic Lesion of CTE

The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of CTE

Based on blinded review of 25 cases of tauopathies, a panel of 7 neuropathologists determined that CTE could be distinguished from AD, PSP, argyrophilic grain disease, CBD, PART, and Parkinson's dementia complex of Guam.

The panel defined a pathognomonic lesion of CTE, defined supportive but non-diagnostic features, and recommended a minimum blocking and staining scheme.

“In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes at the depths of the cortical sulci in an irregular pattern.”

McKee et al, Acta Neuropathologica. 2016;131(1):75-86
Supportive features of CTE

1) superficial NFTs

2) p–tau in CA2 and CA4 hippocampus

3) p-tau in: mammillary bodies, hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus.

4) p-tau thorn-shaped astrocytes (TSA) in the subpial region

5) p-tau dot-like neurites

McKee et al, Acta Neuropathologica. 2016;131(1):75-86
The Second NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

Kevin F. Bieniek, PhD, Nigel J. Cairns, PhD, FRCPath, John F. Crary, MD, PhD, Dennis W. Dickson, MD, Rebecca D. Folketh, MD, C. Dirk Keene, MD, PhD, Irene Litvan, MD, Daniel P. Perl, MD, Thor D. Stein, MD, PhD, Jean-Paul Vonsattel, MD, William Stewart, PhD, FRCPath, Kristen Dams-O’Connor, PhD, Wayne A. Gordon, PhD, Yorghos Tripodis, PhD, Victor E. Alvarez, MD, Jesse Mez, MD, Michael L. Alosco, PhD, Ann C. McKee, MD, and the TBI/CTE group

8 neuropathologists evaluated 27 cases of tauopathies, including 17 CTE cases, using the 2016 NINDS criteria, blinded to all clinical and demographic information.

Bieniek et al, JNEN 2021
The panel confirmed the robustness of the 2016 NINDS criteria with the clarification that the pathognomonic lesion must include ptau in neurons to distinguish CTE from ARTAG.

Purely astrocytic perivascular p-tau pathology represents ARTAG and does not meet the criteria for CTE.

A single pathognomonic lesion is sufficient to diagnose CTE.

Bieniek et al, JNEN 2021
When only a limited number of standard paraffin slides is available, the McKee staging scheme is inconsistent, therefore, when only a limited number of slides are available for evaluation, the panel suggested an algorithm for classifying CTE as low and high stage.
Pathognomonic CTE Lesion:

p-tau aggregates in neurons, with or without thorn-shaped astrocytes, at the depth of a cortical sulcus around a small blood vessel, deep in the parenchyma, and not restricted to the subpial and superficial region of the sulcus.

Diagnostic of CTE

Neuronal p-tau pathology (select all that apply):

- NFT in gyral side adjacent to CTE lesion
- NFT in gyral crest adjacent to CTE lesion
- NFT in superficial cortical laminae (layer II)
- NFT in CA4 of hippocampus (with dendritic swellings)
- NFT in CA2 of hippocampus
- NFT in entorhinal cortex
- NFT in amygdala
- NFT in thalamus
- NFT in mammillary body
- NFT in cerebellar dentate nucleus

Suggestive features (select all that apply):

- Clinical concern
- Tau pathology at sulcal depth NOS
- Superficial cortical NFT without amyloid-β

If none of the above conditions are met, the lesion is not diagnostic of CTE. If at least one condition is met, recommend resampling of 4-8 bilateral cortical sulci including dorsolateral frontal, orbital frontal, superior middle temporal, and inferior temporal gyri.

CTE Lesion?

- <5
- ≥5

If there are <5, then Low CTE. If there are ≥5, then High CTE. If none of the conditions are met, then Not Diagnostic of CTE.
Multiple studies modeling head impact injury show greatest tissue strain, strain rate, mechanical deformation at sulcal depth and perivascular region.

Higher strain and strain rate in sulci compared to gyri
Ghajari et al, Brain 2017, J. Biomechanics 2021

Finite element model of a sulcus and perivasular region during impact injury: greatest mechanical deformation in depth of sulcus and perivascular region.
Liao et al. PNAS 2021
Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules


Article

Structure-based classification of tauopathies

Nature 2019 and 2021
Inflammatory microglia are found in the perivascular CTE lesion and contribute to the ptau pathology.

Increased activated microglia in young football players w RHI (m age 32 yrs) and greater increase in CTE.

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**Cherry J et al., Acta Neuropathol Comm, 2016**
Dose-response between RHI and outcome:
Greater years of football, higher level of play predict:
increased CTE severity, greater ptau burden, greater inflammation

180 football players > 40 yrs with CTE:

- Years of playing football associated with increased white matter rarefaction and NFTs
- White matter rarefaction and NFTs associated with dementia
- Arteriolosclerosis associated with dementia but not years of football.
- Dementia in CTE is likely a result of multiple neuropathologic changes associated with trauma, including white matter rarefaction and NFTs, in addition to non trauma–associated changes, such as arteriolosclerosis.
366 individuals neuropathologically diagnosed with CTE evaluated to determine the association between CTE stage and:

1. Semi-quantitative assessments of AT8 pathology from 14 brain regions
2. Quantitative digital assessment of AT8 pathology across 7 brain regions
3. Age at death
4. Dementia status
5. Years of American football play (proxy for cumulative RHI exposure)

Alosco et al, Acta Neuropathologica 2021
1. Stages of CTE Correlate with Semi-Quantitative Scales of P-tau

Statistically significant across all 14 brain regions:
Dorsolateral frontal cortex ($\rho = 0.65$, $p < 0.001$), Rolandic cortex ($\rho = 0.64$, $p < 0.001$), Inferior Frontal cortex ($\rho = 0.66$, $p < 0.001$), Inferior Parietal cortex ($\rho = 0.60$, $p < 0.001$), Superior Temporal cortex ($\rho = 0.63$, $p < 0.001$), Hippocampus: CA1 ($\rho = 0.51$, $p < 0.001$), CA2 ($\rho = 0.62$, $p < 0.001$), CA4 ($\rho = 0.66$, $p < 0.001$), Entorhinal Cortex ($\rho = 0.66$, $p < 0.001$), Amygdala ($\rho = 0.72$, $p < 0.001$), Substantia Nigra ($\rho = 0.70$, $p < 0.001$), Locus Coeruleus ($\rho = 0.42$, $p < 0.001$).

2. Stages of CTE Correlate with Quantitative P-tau Density

Statistically significant across all brain regions:
DLF gyral crest ($\rho = 0.77$, $p < 0.001$), DLF depths of sulcus ($\rho = 0.73$, $p < 0.001$), CA1 ($\rho = 0.69$, $p < 0.001$), CA2/3 ($\rho = 0.66$, $p < 0.001$), CA4 ($\rho = 0.72$, $p < 0.001$), subiculum ($\rho = 0.70$, $p < 0.001$), and the LC ($\rho = 0.55$, $p < 0.001$). Example:
3. Stages of CTE Correlate with Age at Death

The nature, severity and distribution of CTE-related ptau pathology followed an age-dependent progression

17-100 years old
(mean = 61.75, SD = 18.97)

Age → CTE Stage
(p < 0.001)
4. Stages of CTE Are Associated with Dementia Status (N = 360)

- 216 (60%) determined by consensus panel to have had ante-mortem dementia
- Binary logistic regression controlling for age showed higher CTE stage was associated with increased odds for having dementia (OR = 1.64, 95% CI = 1.19-2.27, p = 0.003); remained after controlling for neurodegenerative and vascular comorbidities

5. Stages of CTE Correlate with Years of American Football Play

Replicated our past work in this larger sample:

- Among the 305 brain donors whose primary sport was American football, more years of American football play was associated with increased odds for having a higher stage of CTE (OR = 1.10, 95% CI = 1.06-1.15, p < 0.001), controlling for age at death.
K-medoid cluster analysis of the semiquantitative scales of p-tau across 14 regions identified 5 clusters of p-tau that conformed to increasing CTE stage (stage 4 had 2 slightly different clusters), age at death, dementia, and years of American football play.
99 male athletes with CTE
range of age at death (20-90 years)
range of disease severity (CTE I-IV)

Quantitative morphologic assessment and multiplex immunofluorescence were used to determine:

- ratio of 4R and 3R tau-containing neurons and astrocytes within the pathognomonic CTE lesion at various stages and ages at death.
The early CTE lesion: 3R and 4R in neurons, 4R predominates.
As age increases (> 60 yrs), increasing 4R astrocytes

- 4R tau cells: CTE stage I 95.8% neurons, stage II 96.1% neurons, stage III 65.6% neurons, CTE IV 69.7% neurons
- 3R was detected only in neurons.
- At age 60–69 years and increasing in each subsequent decade, there is a trend toward increased astrocytes in the CTE lesion
CTE tau consists of 3R and 4R
- P-tau neurons predominate in early CTE
- 4R neuronal tau predominates in early CTE
- P-tau astrocytes only contain 4R tau
- There is a shift from 4R toward 3R tau as the severity of CTE increases
- P-tau astrocytes increase with age (not disease severity)
- Large increase in astrocytic ptau after age 60

Cherry et al, Brain Pathology, 2020
Altered oligodendroglia and astroglia in chronic traumatic encephalopathy

K. Blake Chancellor¹ · Sarah E. Chancellor² · Joseph E. Duke-Cohan¹ · Bertrand R. Huber²,3,4,6 · Thor D. Stein²,4,5,6 · Victor E. Alvarez²,3,4,6 · Benjamin W. Okaty¹ · Susan M. Dymecki¹ · Ann C. McKee²,3,4,5,6

Single-nucleus RNA-seq cell nuclei from DLF white matter

- Oligodendrocytes were reduced in CTE and altered in relative proportions of subtypes compared to controls
- CTE-enriched oligodendrocytes showed more transcripts relevant to iron metabolism and cellular stress response
- CTE tissue also demonstrated excessive iron accumulation histologically
• Total astrocyte number indistinguishable between CTE and control samples, but transcripts associated with neuroinflammation were elevated in CTE astrocytes compared to controls.
Using a biosensor assay to independently quantify tau seeding compared to AT8 phospho-tau pathology in 11 brain regions from 27 patients with CTE, 5 with other tauopathies, and 5 negative controls, tau seeding was detected primarily in CTE stage III and IV and restricted to the amygdala, thalamus, and basal ganglia.

The relationship of seeding to the staging of the disease remains unclear.
Among 266 football players:

- Risk of developing CTE increased by 30 percent per year played
- For each 2.6 additional years of football, odds of developing CTE doubled
- Among those w CTE, for each additional 5.3 yrs, the odds for severe CTE doubled
- Those who played < 4.5 yrs were 10 X less likely to develop CTE than those who played longer
- Those who played >14.5 yrs were 10 X more likely to develop CTE than those who played less

Using simulation and inverse probability weighting, accounting for all degree of selection bias, the strength of the duration of play-CTE relationship remained consistent

Mez et al, Annals Neurology 2019
Aaron Hernandez: 27 year old NFL player
Brain weight: 1573 grams
Ventricular enlargement

Normal 27 year old

Aaron Hernandez
Normal 27 year old

Ventricular enlargement

Atrophy of the fornix

Aaron Hernandez
• Neuropathological abnormalities of this magnitude are unusual in young individuals with CTE.
• Among 348 donors neuropathologically diagnosed with CTE in the UNITE Brain Bank with recorded ratings for septal fenestrations, approximately 30% had evidence of septal fenestrations.
• This case demonstrates the first instance of CTE with septal fenestrations under the age of 40 in our experience.
Aaron Hernandez

CTE, stage III:
with severe frontal lobe involvement
moderate involvement of temporal lobe and amygdala
Inflammatory microglia are present within the CTE lesion

<table>
<thead>
<tr>
<th></th>
<th>Lba1</th>
<th>Inflammatory Marker</th>
<th>AT8</th>
<th>Merge</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>B</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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<tr>
<td>C</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>D</td>
<td><img src="image1.png" alt="Image" /></td>
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<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>

**Legend:**
- CD68
- CD11c
P-tau aggregates in neurons and neuronal processes in CTE lesions in young individuals
4R tau is the predominant isoform
Clinicopathological case series: 158 brain donors ≤ age 34 years

- 158 brains from contact sport athletes 34 years or younger at the time of death, mean 24.6 years

- 78 (49%) diagnosed with CTE:
  Stage 1  n = 43  (55.1%)
  Stage 2  n = 32  (41.0%)
  Stage 3  n = 3   (3.8%)

80 negative for CTE
# Young CTE

## Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total sample (n=158)</th>
<th>No CTE (n=80)</th>
<th>CTE (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of death</strong></td>
<td><strong>Mean</strong> 24.63 5.33</td>
<td><strong>Mean</strong> 22.11 5.44</td>
<td><strong>Mean</strong> 27.19 3.80</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td><strong>n</strong> 6 3.8</td>
<td><strong>n</strong> 6 7.5</td>
<td><strong>n</strong> 0 0</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td><strong>n</strong> 6 3.8</td>
<td><strong>n</strong> 6 7.5</td>
<td><strong>n</strong> 0 0</td>
</tr>
<tr>
<td><strong>Primary cause of death</strong></td>
<td><strong>n</strong> 71 44.9</td>
<td><strong>n</strong> 40 50</td>
<td><strong>n</strong> 31 39.7</td>
</tr>
<tr>
<td>Suicide</td>
<td><strong>n</strong> 71 44.9</td>
<td><strong>n</strong> 40 50</td>
<td><strong>n</strong> 31 39.7</td>
</tr>
<tr>
<td>Accidental Overdose</td>
<td><strong>n</strong> 17 10.8</td>
<td><strong>n</strong> 9 11.3</td>
<td><strong>n</strong> 8 10.3</td>
</tr>
<tr>
<td>Injury</td>
<td><strong>n</strong> 14 8.9</td>
<td><strong>n</strong> 6 7.5</td>
<td><strong>n</strong> 8 10.3</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td><strong>n</strong> 4 2.5</td>
<td><strong>n</strong> 2 2.5</td>
<td><strong>n</strong> 2 2.6</td>
</tr>
<tr>
<td>Infection</td>
<td><strong>n</strong> 3 1.9</td>
<td><strong>n</strong> 0 0</td>
<td><strong>n</strong> 3 3.8</td>
</tr>
</tbody>
</table>
# Young CTE

## Demographics

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<tr>
<th>Demographics</th>
<th>Total sample (n=158)</th>
<th>No CTE (n=80)</th>
<th>CTE (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Athletic History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary sport played</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>American football</td>
<td>107 (68)</td>
<td>45 (56)</td>
<td>62 (80)</td>
</tr>
<tr>
<td>Ice Hockey</td>
<td>20 (13)</td>
<td>10 (13)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Soccer</td>
<td>12 (8)</td>
<td>9 (11)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Wrestling</td>
<td>7 (4)</td>
<td>6 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rugby</td>
<td>2 (1)</td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other exposure</td>
<td>3 (2)</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Duration of American Football play</strong></td>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td>Years</td>
<td>9.77</td>
<td>4.70</td>
<td>7.97</td>
</tr>
<tr>
<td>Highest level of sport play</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Professional</td>
<td>25 (16)</td>
<td>3 (4)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>Semi-professional/Juniors</td>
<td>10 (6)</td>
<td>7 (9)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>College</td>
<td>38 (24)</td>
<td>9 (11)</td>
<td>29 (37)</td>
</tr>
<tr>
<td>High school</td>
<td>65 (41)</td>
<td>45 (56)</td>
<td>20 (26)</td>
</tr>
<tr>
<td>Youth</td>
<td>16 (10)</td>
<td>12 (15)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>
Superior frontal cortex

Ptau tangles

blood vessel
**Fig. Association Between CTE Stage and Regional P-tau Progression.** Heat map of semi-quantitative p-tau pathology (0 to 3, 3 most severe) for 14 brain regions

<table>
<thead>
<tr>
<th>CTE Stage</th>
<th>N (%)</th>
<th>DLF</th>
<th>RC</th>
<th>IF</th>
<th>IP</th>
<th>ST</th>
<th>CA1</th>
<th>CA2</th>
<th>CA4</th>
<th>EC</th>
<th>Amygdala</th>
<th>Thalamus</th>
<th>SN</th>
<th>LC</th>
<th>Dentate</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>79 (55.6)</td>
<td>0.09</td>
<td>0.00</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
<td>0.08</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
<td>0.16</td>
<td>0.00</td>
<td></td>
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<tr>
<td>I</td>
<td>35 (24.6)</td>
<td>1.06</td>
<td>0.23</td>
<td>0.28</td>
<td>0.50</td>
<td>0.48</td>
<td>0.14</td>
<td>0.03</td>
<td>0.07</td>
<td>0.29</td>
<td>0.17</td>
<td>0.06</td>
<td>0.03</td>
<td>0.64</td>
<td>0.00</td>
</tr>
<tr>
<td>II</td>
<td>25 (17.6)</td>
<td>1.88</td>
<td>1.04</td>
<td>1.18</td>
<td>1.35</td>
<td>1.74</td>
<td>0.68</td>
<td>0.21</td>
<td>0.52</td>
<td>1.33</td>
<td>1.23</td>
<td>0.63</td>
<td>0.54</td>
<td>1.73</td>
<td>0.04</td>
</tr>
<tr>
<td>III</td>
<td>3 (2.1)</td>
<td>3.00</td>
<td>2.00</td>
<td>1.00</td>
<td>2.00</td>
<td>2.33</td>
<td>2.00</td>
<td>0.33</td>
<td>1.33</td>
<td>1.67</td>
<td>2.33</td>
<td>1.00</td>
<td>1.33</td>
<td>2.33</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td>142</td>
<td>0.77</td>
<td>0.28</td>
<td>0.31</td>
<td>0.40</td>
<td>0.50</td>
<td>0.23</td>
<td>0.06</td>
<td>0.15</td>
<td>0.41</td>
<td>0.34</td>
<td>0.16</td>
<td>0.13</td>
<td>0.62</td>
<td>0.01</td>
</tr>
</tbody>
</table>
CTE in subjects ≤ 34 years

- Preliminary results show that there are significantly more perivascular hemosiderin-laden macrophages in the frontal and temporal white matter in CTE compared to non-CTE.
Subpial TSA at sulcal depths

• Only 19% of the young subjects with CTE had p-tau thorn-shaped astrocytes (TSA) in the glial limitans at the depth of the sulcus; subpial TSA were not found in non-CTE subjects
None of the 158 young subjects, with or without CTE, showed any immunopositivity for Aβ, either as plaques or amyloid angiopathy.

One subject had a-synuclein Lewy bodies: 27-year-old with Stage 2 CTE - rare LB in the medulla

9 of the 78 with CTE (12%) had immunopositivity for phosphorylated TDP-43, primarily as neurites; 3 were diagnosed with motor neuron disease
Case 1:
Brain weight: 1374 grams
Superior frontal cortex

*depth of sulcus

AT8
Superior frontal cortex

vessel
Inferior parietal
Inferior parietal
Rolandic
amygdala
Substantia Nigra  

Locus Coeruleus
Case 1: Diagnosis?
Case 1

CTE Stage II:

- mild frontal atrophy
- small cavum septum pellucidum
- perivascular lesions in superior frontal, dorsolateral frontal, Rolandic, inferior parietal and inferior temporal cortices.
- Moderate neurofibrillary degeneration - locus coeruleus
- Mild neurofibrillary degeneration - substantia nigra and amygdala
Case 1

- 31 years old
- Football for 20 years as a safety: started at age 6, including 2 years AFL and 2 years NFL.
- At 21, knee surgery and prescribed hydrocodone-acetaminophen, became dependent.
- At 24, memory problems
- At 25, progressive attentional difficulties, anxiety, depression.
- Dxd as bipolar vs. schizofffective. Delusions and hallucinations, manic episodes.
- At 26, daily headaches
- Death age 31 from MVA
Case 2
Brain weight: 1475 grams
Superior frontal cortex
Superior frontal cortex
Superior Temporal Cortex
Inferior Frontal Cortex
Hippocampus

CA4/CA3

CA4
Amygdala
Substantia nigra
Locus Coeruleus
Aβ

Bielschowsky

Thal Stage 4, Sparse Neuritic Plaques
Case 2: Diagnosis?
Case 2:

CTE Stage III:

- Mild frontal, parietal, temporal atrophy
- Cavum septum pellucidum
- Multiple pathognomonic lesions cerebral cortex
- Widespread p-tau lesions: bank and crest of cerebral cortex, dense NFTs in CA4, CA1, entorhinal cortex, amygdala, substantia nigra, locus coeruleus

Without prominent neuronal loss
Without involvement of basis pontis, dentate nucleus cerebellum
Case 2:

1. CTE Stage III
2. Alzheimer’s Disease Neuropathological Change:
   NIA/Reagan: Intermediate likelihood
   Thal 4, A3; Braak 5, B2; CERAD 1, C1
3. LATE Stage 3
4. White Matter Rarefaction, moderate
5. Arteriolosclerosis
Case 2:

63 years old
Football for 21 years as a middle linebacker
  4 years in the NFL
  3 years in the USFL
At 56, increasingly short fuse
Late 50s, lost interest in his hobbies
Sleep difficulties and sleepwalking episodes
Worsening depressed mood and mood lability
At age 61, memory problems and mild cognitive impairment
At age 62-63, more isolated, childlike and immature
Death by suicide
Case 3
Brain weight: 1092 grams
Rolandic cortex
Rolandic cortex
Rolandic cortex
Case 3: Diagnosis?
Case 3:

1. Chronic Traumatic Encephalopathy, stage IV
2. Features of PSP:
   Dense NFT in motor nuclei: basis pontis, red nucleus, subthalamic nucleus, dentate nucleus, globus pallidus, inferior olives, spinal cord
   Unclassifiable astrocytic inclusions
3. LATE
Case 3:

75 year old
Football for 28 years including 12 years as linebacker in NFL
At age 69, his driving declined, hesitations in making turns
Age 70, slowed, effortful movements
Age 71, anxious and occasional falls
Asymmetric poor functioning of the left side while walking
Impulsive changes in position triggered falls
Severe apraxia
By 73, he could not button a shirt or put a letter into an envelope
Word-finding difficulty, angered easily with perseveration
Impulsivity, poor insight.
By 75, episodes of festination, occasional choking
Hypophonic with mild masking of left face, bilateral tremor,
Severe apraxia on the left
Difficulty initiating voluntary eye movements
Increased axial and appendicular tone L>R
Frontal release signs present.
Gait was wide-based and unsteady
Cognitive impairment with relatively preserved memory
Death from aspiration pneumonia
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