Pathology of Chronic Traumatic Encephalopathy

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The speaker does not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Is CTE and dementia pugilistica the same condition?

- Martland, HS. Punch Drunk. JAMA. 1928;91(15):1103-1107
  - 15 cases
  - Many co-morbidities
75 year old boxer
Chronic Traumatic Encephalopathy

- A *progressive tauopathy*
- Pattern/distribution of tau distinguish from age and known neurodegenerative conditions.
  - Depth of sulci, perivascular, superficial cortical laminae, medial temporal lobe, brainstem tegmentum
  - Axonal varicosities
  - Often with Cavum septum pellucidum, fenestrated septum pellucidum
- Variable neurobehavioral symptoms
- Empirical association with contact sports
CTE versus DP

- *Age at onset, death
- **Exposure**
  - DP – 50% with 300+ bouts
  - CTE - ?
- **Progression**
  - 30% for DP
  - 3 cases for CTE
- **Clinical**
  - DP – neurologic
  - CTE – neuropsychiatric and behavioral
- **ApoE**
  - DP – weak association with ApoE 4 (not confirmed)
  - CTE – no association
- **Pathology**
  - DP – cerebellar scarring, extensive medial temporal tau, degeneration of SN, LC
  - CTE - Stages


JAMA 1984;251(20):2676-2679
Paradigm

“TBI”

“Neuroinflammation”

Tau phosphorylation

Cell to cell propagation (prion like?)

Disease *progression*

Neuropsychiatric changes
Problems

• Biomechanical substrate of “CTE” unknown

• Role of concussion unclear

• Pathology of concussion, unclear
  – ? Related to diffuse traumatic axonal injury
    • Axonal injury, including fornices
Problems

• Toxicity of phosphorylated tau is doubtful
  – Survives within neurons for decades
  – Binds adducts (Advanced glycation, lipid peroxidation)
  – Sequesters heavy metals, free radicals
  – Accumulates in everyone with age
  – Experimental data showing ptau accumulation with no adverse consequences

• Kinetics of tau accumulation in CTE is unclear

PHOSPHORYLATED TAU:
TOXIC, PROTECTIVE, OR NONE OF THE ABOVE

Rudy J. Castellani, Akihiko Nunomura,
[...], and Mark A. Smith
“Tauopathies”


- Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)
- Alzheimer's disease
- Aging
- Progressive supranuclear palsy
- Pick's disease
- Argyrophilic grain dementia
- Corticobasal degeneration
- Progressive subcortical gliosis
- Amyotrophic lateral sclerosis/parkinsonism-dementia complex
- Diffuse neurofibrillary tangles with calcification
- Dementia pugilistica (Chronic traumatic encephalopathy)
- Tangle-only dementia
- Down syndrome
- Gerstmann-Straussler-Scheinker disease
- Hallervorden-Spatz disease
- Creutzfeldt-Jakob disease
- Multiple system atrophy
- Niemann-Pick disease type C
- Prion protein cerebral amyloid angiopathy
- Subacute sclerosing panencephalitis
- Myotonic dystrophy
- Non-guamanian motor neuron disease with neurofibrillary tangles
- Postencephalitic parkinsonism
- Meningioangiomatosis
- Tuberous Sclerosis
Tau in locus ceruleus

• P-tau is observable in the locus ceruleus as early as the first decade of life
  – Braak H, et al. JNEN 2011;70(11);960-969

• Locus ceruleus is “unsurpassed” in the diffuseness of its connections
  – Jones BE. Prog Brain Res 1991;88:15-30

• Cell to cell propagation of (toxic) ptau as an in vivo phenomenon is therefore problematic

Projections of locus ceruleus
http://corticalchauvinism.files.wordpress.com/2013/03/locus_coeruleus.gif
Tau immunostain - locus ceruleus, 44 year old man
Tau in the cerebral cortex in healthy young people; with “protective” Apolipoprotein E genotype (2/3)

Braak Stage | Dementia
---|---
0 | 0/11*
I | 0/13*
II | 0/17*
III | 5/10*
IV | 5/10*
V | 8/8**
VI | 14/14**

*Variable amyloid  
**Extensive amyloid
Phosphorylated tau = localized reaction to sublethal injury; occurs in everyone as a function of age
Problems

- Neuropathology of neurodegenerative diseases predicts neurologic signs only with difficulty
  - Alzheimer disease versus cognition?
    - Updated NIAA Alzheimer disease criteria specifically excludes clinical history.
    - Independent examination of brains of elderly does not reliably predict cognition, presence or absence of dementia.
  - Frontotemporal dementia
    - behavioral versus semantic versus primary progressive aphasia?
  - Lewy body diseases?
  - Functional disturbances?
    - schizophrenia, autism, mood disorders, impulse control, suicide
Problems

• No evidence that contact sports causes neurodegenerative disease, or is a risk for genuine neurodegenerative disease
CTE?

Presence of “CTE” with single traumatic events

Increased tau in depth of sulcus      Perivascular tau      Tau in the margin of a contusion

Professional football player, age 41
Localized tau in the amygdala in a professional football player
41 year old offensive lineman with a normal brain for age, and no neuropsychiatric disturbances

50 year old offensive lineman with CTE (Neurosurgery 57:128-134, 2005)

Tau (AT8) immunostain (6 µm), retired NFL players
Is focus on proteins such as tau and amyloid beta distracting us from more relevant pathophysiological processes?
Conclusions

• What we know:
  – CTE is a pattern of phosphorylated tau that appears to differ from aging on the one hand, and neurodegenerative diseases on the other
  – CTE is not a neurodegenerative disease

• What we don’t know:
  – Role of concussion, if any, in producing CTE
  – Prevalence of the changes in various types of contact sports
  – Whether contact sports carries a small risk of Alzheimer’s disease, ALS, or other neurodegenerative diseases
  – The degree to which benefits of participation in contact sports balances the risks.
  – Whether protein templating is relevant to humans in vivo

• What we have no business discussing:
  – A potential causative role of ptau in suicide, impulse control, domestic disarray or any other functional disturbance.