Chronic Traumatic Encephalopathy & FTD

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Research Support

- NIA
- FTLD Program Project Grant, "Genes, Images Emotions", (P01)
- Alzheimer’s Disease Research Center (P50)
- T32 & K08/23 Training Grants
- NINDS
- iPSC derived neurons in FTD (Yadong Huang, Fen Biao-Gao)
- AAN Fellowships
- Philanthropy
  - Consortium for Frontotemporal Research
  - Tau Consortium
  - Hellman family
  - Hillblom & John Douglas French Foundation
- Many, many brilliant Foreign Scholars

Overview

- TBI – risk for dementia
- CTE – overview and NFL players
- FTD
  - Overview
  - Key to diagnosis
  - Misdiagnosis
  - Criminality
  - Slow FTD
  - Genetics, Imaging, Treatment
**TBI: Growing Epidemic?**

- 1.6 to 3.8 sports-related concussions/year
- Headache, dizzy, nausea, foggy, confusion, emotional instability, amnesia
- Mild concussion 2–14 days
- Neuropsychological function within 5 days back to normal
- Chronic repetitive injury—“chronic traumatic encephalopathy”


**General Principles**

- Brain regions sit against bone most vulnerable
  - Temporal (memory, behavior)
  - Frontal—drive, inhibition, mood
- Shearing of white matter (strich injury)
  - Cognitive deficits
  - Emotional deficits
  - Motor deficits
- Static injury
  - Slow healing

**Risk Rate Previous Minor TBI**

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>AD</th>
<th>PD</th>
<th>Depression</th>
<th>Mixed affective</th>
<th>Bipolar</th>
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<tbody>
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<td>0.5</td>
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<td>1</td>
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<td>2</td>
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<td>2.5</td>
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</tbody>
</table>

Perry et al submitted

**Traumatic Brain Injury & Cognitive Impairment**

TBI increases risk of cognitive aging

Case Control Head Injury & AD Risk Fleminger et al, JNPP, 2003
Cohort Study TBI & Dementia

- 188,764 U.S. veterans age ≥55 dementia free

Measures
- TBI diagnoses during baseline (ICD-9)
- Dementia diagnoses during 9 years follow-up
- TBI: 0.65% (N=1229)
  - Intra-cranial injury: 43%
  - Skull fracture: 21%
  - Late effect of head injury: 14%
  - Post-concussion syndrome: 4%
  - Unspecified head injury: 27%

Barnes…Yaffe, Neurology, 2014

TBI Severity Risk Dementia

Barnes…Yaffe, et al Neurology, 2014

Summary

- TBI 60% increase risk of dementia
- Age of dementia onset 2 years earlier in TBI compared to those without TBI
- Additive association observed between TBI and other dementia risk factors
- Older adults with blast-related injuries may need additional study

Dementia Pugilistica

- 1928 Martland “punch-drunk” repeated head blows
- 1937 Millspaugh coined “dementia pugilistica”
- 1962 Corsellis “psychopathic deterioration boxers”
- 1973 Corville 3 stages
  - 1st stage: affective disturbances, psychotic symptoms, social instability, erratic behavior
  - 2nd stage: memory loss and mild PD
  - 3rd stage: dementia, PD, shuffling gait, dysarthria, dysphagia and ocular abnormalities.
CTE

- Clinical symptoms begin long latency—several years to several decades.
- Initial: irritable, impulsive, aggressive, disinhibited, depressed, amnesia, suicide
- Later: slow cognitive deficits to dementia
- Incidence?
- 321 football players died 2008–2010, 12 had autopsy at BU; 12 had CTE.

McKee, Daneshvar, Alvarez & Stein 2014
Stein, Alvarez & McKee 2014

Serum & CSF Biomarkers Trauma

- Hockey players: serum alpha-pectrin-n-terminal fragment ↑1 hr post-concussion.
  - ↑12 hrs - 6 days, 20 players withheld play > 6 days, SNTF levels rose 12-36 hrs higher than less severe concussions (p=.004). (Siman J Neurotraum 2014)
- Serum levels tau-C higher post-concussion samples. (Siman J Neurotraum 2014)
- CSF neurofilament-derived protein ↑80% Olympic boxers post-bout (Neselius et al PLOS 2012-14)

McKee, Daneshvar, Alvarez & Stein 2014
Stein, Alvarez & McKee 2014

Aβ Imaging in TBI

Hong et al., JAMA Neurology 2013
UCSF NFL Cohort

UCSF MAC NFL Cohort

- 20 retired professional American football players evaluated to date
  - 19 symptomatic, 1 asymptomatic
  - FDG and Amyloid PET being obtained on players

3 Clinical Phenotypes

1. Chronic post-concussive syndrome
2. Delayed-onset behavioral syndrome
3. Delayed-onset cognitive/motor syndrome

1: Chronic Post-Concussive Syndrome

- 33 M 6 yrs forgetful, severe migraines, onset halfway into 8-yr NFL career, early retirement
- Also irritability, depression, insomnia
- Variable attention, low-avg episodic memory, impaired phonemic fluency
- MRI brain unremarkable
- Improved with aggressive migraine treatment
- After 2 years, migraine well-controlled, but cognitive symptoms worse & new symptom brief confusional episodes AM awakening
2: Delayed-Onset Behavior Syndrome

- 65M 8 yrs rage attacks triggered by EtOH, onset 27 years after retirement from football
- Also mild depression, insomnia, moderate parkinsonism, fine postural hand tremor
- Impaired verbal fluency, false positive rate on delayed verbal memory recognition
- Inpatient EEG normal, lamotrigine resolved rage attacks despite continued EtOH use
- After 2 years, cognitive symptoms worse and patient meets criteria for mild dementia

3: Delayed-Onset Cognitive Syndrome

- 73M, 2 yrs difficulty short-term memory, word-finding, navigation, multi-tasking, onset 34 years after retirement.
- Mild depression, insomnia, mild parkinsonism, no tremor
- Impaired episodic memory, working memory, spatial localization
- No improvement cholinesterase-inhibitor
- Over 2 years, progressed MCI to dementia

3: Amyloid Neg, APOE E3/E3

- MRI hippocampal & mammillary body atrophy, CSP
- FDG-PET medial temporal & parietal hypometabolism
- Amyloid-PET

Case 2

MRI
4: Delayed-Onset Cognitive Syndrome

- 51M 3 yrs trouble **spatial skills, calculation, problem-solving**, 25 years after retirement
- Irritability, anxiety, insomnia, tremor
- Bad working memory, spatial skills, normal episodic memory, “d” fluency
- Improved cholinesterase-inhibitor
- After 1 year, stable diagnosis of MCI

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Case 4: Amyloid Pos, APOE E3/E4

**MRI:** mild parietal atrophy, CSP, patchy periventricular WM

**FDG-PET:** posterior cingulate, precuneus, parietal hypometabolism

**Amyloid-PET**

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5: 68 Retired NFL Slow Neurologic Decline

**At risk CTE Aβ PET ([11C]PIB)**

**At risk CTE Tau PET ([18F]AV1451)**

**Mean controls Tau PET ([18F]AV1451)**

**Concussion, Post-concussion Syndrome, CTE & Neurodegeneration**

**Symptom overlap**

**Pathological overlap**

Tartaglia et al 2014
Ongoing Questions
- Relationship AD, FTD, PSP/CBD, ALS
- Can we prevent in traumatic sports?
- Are there other factors
  - Obesity
  - Sleep apnea
  - Steroid use
  - Drugs, alcohol, chronic pain meds
- What is role of anti-tau therapies

Conclusions
- CTE lurking epidemic: tau as major target
- Tau PET will have high impact
- Tau therapies are underway
- Need more research

Overview
- FTD clinical syndrome predicts pathology
- Best predictors bvFTD (n=206) vs. AD (n=678) across stages dementia (CDR)
  - Behavior
  - Executive control
- FTD misdiagnosis: under and over diagnosis - 3578 charts: 19% bvFTD
- Criminal behavior and FTD
- Slow FTD
- Genetic FTD—the early stages & tau PET
- Clinical basic science consortia

Arnold Pick
Aphasia in dementia, 1892
Pick body (Alzheimer), 1911
3 types frontotemporal dementia

- Behavioral variant
- Language variants
  - Semantic variant
  - Nonfluent variant

Strongly genetic, Multiple pathologies: TDP43, Tau, FUS

Rarely genetic Usually TDP-C, Autoimmune?

Usually Tau or TDP-A

International bvFTD Research Criteria

1. Early (2–3 yrs) behavioral disinhibition
2. Early (2–3 yrs) apathy or inertia
3. Early (2–3 yrs) loss of emotional reactivity/sympathy & empathy
4. Perseverative, stereotyped or compulsive/ritualistic behavior
5. Hyperorality and dietary changes
6. FTD neuropsychological profile
7. Frontal and/or anterior temporal atrophy on MRI
8. Presence of known mutation

Regions Involved Emotion, Reward, Social Cognition

- Insula
- Anterior Cingulate
- Amygdala
NPI bvFTD & AD by Stage
Neuropsychiatry symptoms across clinical dementia rating (CDR) in bvFTD (206) & AD (678)

Ranasinghe & Rankin Submitted

Executive Control bvFTD vs AD

Performance executive tasks, emotion recognition increasing disease severity AD (n= 678) vs bvFTD (n=206)

Ranasinghe & Rankin submitted

Psychiatric Misdiagnosis
Rates of Psychiatric Diagnosis within Each Neurodegenerative Dx


Correctly Dx vs Misdiagnosed

UCSF not bvFTD
UCSF bvFTD

NPI subscore *:p<0.05 **:p<0.01

3578 Charts Shimagawa, Cattaroe, et al. under review
147 (60%) misdx
Amyloid PET Outperforms FDG-PET Differentiating AD vs. FTD

47 autopsy-proven cases
Amyloid (PIB) PET visual reads
100% sensitivity
90% specificity
FDG-PET visual reads
87% sensitivity
79% specificity

Criminality Across Diagnoses

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Total n</th>
<th>Frequency of criminality: n (%)</th>
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</thead>
<tbody>
<tr>
<td>bvFTD</td>
<td>171</td>
<td>64 (37.4%)</td>
</tr>
<tr>
<td>svPPA</td>
<td>89</td>
<td>24 (27%)</td>
</tr>
<tr>
<td>AD</td>
<td>545</td>
<td>42 (7.7%)</td>
</tr>
<tr>
<td>HD</td>
<td>30</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>VaD</td>
<td>61</td>
<td>9 (14.8%)</td>
</tr>
<tr>
<td>PSP</td>
<td>63</td>
<td>4 (6.4%)</td>
</tr>
<tr>
<td>CBS</td>
<td>73</td>
<td>4 (5.5%)</td>
</tr>
<tr>
<td>MCI</td>
<td>243</td>
<td>8 (3.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>1122</td>
<td>43 (3.8%)</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>2397</strong></td>
<td><strong>204 (8.5%)</strong></td>
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Criminal Behavioral Classification in bvFTD, svPPA & AD

<table>
<thead>
<tr>
<th>bvFTD</th>
<th>svPPA</th>
<th>AD</th>
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<tbody>
<tr>
<td>37.4%</td>
<td>27%</td>
<td>7.7%</td>
</tr>
<tr>
<td>early</td>
<td>early</td>
<td>late</td>
</tr>
<tr>
<td>sexual advances, theft, public urination, violence</td>
<td>theft, traffic violation</td>
<td>traffic violation, trespassing due to wandering</td>
</tr>
<tr>
<td>disinhibition, impulsivity, reward/punishment dysfunction</td>
<td>compulsive attraction to visual stimuli, disinhibition</td>
<td>cognitive dysfunction</td>
</tr>
<tr>
<td>anterior insular, orbitofrontal, ventral striatum</td>
<td>bilateral anterior temporal lobe, orbitofrontal, ventral striatum</td>
<td>hippocampus, parietal lobe</td>
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Main FTD Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>C9orf72</th>
<th>MAPT</th>
<th>GRN</th>
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<tbody>
<tr>
<td>Age of DX</td>
<td>56</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>Clinical</td>
<td>FTD-ALS</td>
<td>FTD, PSP, CBD</td>
<td>FTD, PA, AD, CBD</td>
</tr>
<tr>
<td>MRI</td>
<td>Mild, dorsal, occipital, cerebellar</td>
<td>Classical frontotemporal</td>
<td>Asymmetric frontotemporal</td>
</tr>
<tr>
<td>Unique clinical</td>
<td>ALS, thalamic</td>
<td>Symmetry, addiction</td>
<td>Overlap with AD</td>
</tr>
<tr>
<td>Unique biology</td>
<td>RNA-mediated</td>
<td>4r tauopathy</td>
<td>Haploinsufficiency, Links to AD?</td>
</tr>
</tbody>
</table>
How Many *Individuals* Do You Follow with fFTLD or a Related Disorder?

Genetic FTD: Early Changes

- Selfishness
- Passivity/withdrawal, social isolation
- Aggression/antisocial behaviors
- Alcohol, drug & other addictions
- Compulsions (sometimes creative ones)
  - Art
  - Business
- Odd affiliations (changes in self)
- Loss of empathy for others

Early Psychiatric Diagnoses

- Bipolar illness
- Schizophrenia
- Major Depression
- Addiction Disorder (multiple types)
- Personality Disorders
  - Borderline
  - Passive-aggressive
  - Dissociative syndrome
  - Antisocial
  - Schizoidal
  - Schizotypal

Slow bvFTD (bvFTD Phenocopy)

- Mild bvFTD syndrome
- Slow or minimally progressive
- Neuropsychological function can be normal
- MRI normal
- Primary psychiatric?
VBM (tissue loss) bvFTD Phenocopy

Khan et al. JNNP 2012

Abnormalities Medial Pulvinar Thalamus Associated Salience Network Disruption C9orf72+ bvFTD

Lee S E et al. Brain 2014

Tau Consortium 2014

PSP Dorsal Midbrain Tegmental Network

AV1451 PET

Functional Connectivity

Gardner et al. Ann Neurol 2013
Tau Spreads Like a Prion

Immunostain Neurons (42 Days) Derived from Isogenic Tau-A152T-hiPSCs

Tau Clearance

Therapeutic Approaches 2015

- Tau antibody for PSP & other tau forms of FTD (David Holtzman)
- Decrease acetylation, phosphorylation tau or increase clearance of tau (Ana Maria Cuervo)
- NIFTD & 4RTNI finish (good biomarkers for trials) (Howard Rosen, Adam Boxer)
- Tau imaging agents (Gil Rabinovici, Bill Jagust)
Trans-cellular propagation of Tau

Aggregation occurs via transfer fibrils within cell medium

Tau propagation model:
- protein aggregate donor cell escapes cell (A),
- enters recipient cell (B),
- directly contacts natively folded protein (C) amplify the misfolded state (D)
- cell-cell movement mediated by fibrils released into the medium
- fibrils in extracellular space targeted by anti-tau antibody

Holtzman & Diamond
Genetic Families: MAC Cohorts

<table>
<thead>
<tr>
<th>Gene in Family</th>
<th>Kindred</th>
<th>Carriers</th>
<th>Non-Carriers</th>
<th>Individual untested</th>
<th>Total Individuals</th>
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<tbody>
<tr>
<td>C9ORF72</td>
<td>38</td>
<td>74</td>
<td>18</td>
<td>11</td>
<td>103</td>
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<tr>
<td>GRN</td>
<td>24</td>
<td>46</td>
<td>29</td>
<td>2</td>
<td>75</td>
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<tr>
<td>MAPT</td>
<td>9</td>
<td>16</td>
<td>9</td>
<td>4</td>
<td>29</td>
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<tr>
<td>TDP-43</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>7</td>
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</table>

*We have 11 carriers with the rare variant $MAPT_A152T$*

bvFTD Misdiagnosis

- Alzheimer’s disease (CSF, amyloid imaging)
- Primary psychiatric diagnosis (MRI)
- Movement disorders (SCAs)
- Prion disorders (MRI)
- CTE (take trauma history seriously)
- Normal/low pressure syndromes (MRI)
- Metabolic syndromes (B12)
- Vascular dementia (MRI)
- Mixed pathology
- Immune-related