**Advances in Neurology 2010**

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**Neuropathology Inclusions**

- **AD** – Plaque (Aβ-42, 1984), Tangle (tau, 1986)
- **PD** – Lewy body (α-synuclein, 1998)
- **FTD** - Pick body (tau, 1990), Ubiquitin (TDP-43, 2006), Ubiquitin (FUS, 2009)
- **ALS** – Ubiquitin (TDP-43, 2006, FUS, 2009)
- **CJD** – Prions (1982)

**Models of Degenerative Dementia**

- All degenerative dementias have:
  - Genetic and sporadic form
  - Cell culture and animal model
  - Preclinical, early symptomatic and symptomatic phase
  - Abnormal protein aggregation
**FTD Versus AD Atrophy**

A

- Syndrome-specific regional atrophy patterns: patients vs. controls
- **AD**
- bvFTD
- SD
- PNFA
- CBS

B

- Intrinsic functional connectivity networks: healthy controls

C

- Structural covariance networks: healthy controls

- Seeley et al, Neuron 2009

**FTD atrophy by clinical stage**

- Early FTD
  - CDR 0.5
    - N = 15
  - CDR 1
    - N = 15
  - CDR 2-3
    - N = 15

- FTD atrophy by clinical stage

**Von Economo Neurons ACC & FI**

- Allman et al, 2006
**International Research Criteria for FTD**

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 and 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

**Flanker Task**

- Objective is for participant to identify whether central arrow points to either left or right.
Frequency of Behavioral Disorders in AD and FTD (Neuropsychiatric Inventory)

- Delusions
- Hallucinations
- Agitation
- Depression
- Anxiety
- Elation
- Apathy
- Disinhibition
- Irritability
- Aberrant MB
- Sleep DO
- Eating DO


Three variants of PPA

- Three variants of primary progressive aphasia (PPA) have been described
  - Non-fluent variant
  - Semantic variant or semantic dementia
  - Logopenic variant

Organization

- Overview of molecules
- bvFTD anatomy
- International Research Criteria
- FTLD molecules
- CBD
- Treatment

Amyloid Imaging

AD

FTLD

Progressive Non-Fluent Aphasia

- Non-fluent spontaneous speech
  - Decreased words, phrase length
  - Agrammatism
  - Verbal apraxia
- Abnormalities in executive function
- Humble, behaviorally normal
- Many show asymmetric Parkinsonism

PNFA: Speech Apraxia

PNFA: Alien Hand

MRI Evolution: PNFA to CBD
Temporal Syndromes (Neary SD)
- Progressive fluent language disorder
  - Loss of word meaning
  - Semantic paraphasia and/or
- Progressive disorder in facial recognition and empathy

Logopenic variant: PET-PIB study

- 59 yo F
- 63 yo M
- 60 yo F
- 56 yo F

Semantic Variant

Frontotemporal dementia: pathology & genes
- Tau-positive
- Ubiquitin-TDP-43-positive, Tau-negative
- Ubiquitin-positive, Tau/TDP-43-negative, FUS-positive

Chromosome 17q21: MAP-T
- Microtubule stability and axoplasmic transport
- Cell proliferation and repair
- Regulation of transcription, RNA splicing and export

Chromosome 17q21: PRGN

Chromosome 16: FUS/TLS

Ubiquitin-positive, Tau/TDP-43-negative, FUS-positive

Hutton, Nature 1999
Baker, Nature 2006
Cruts, Nature 2006
Neumann, Science 2006
Kwiatkowski, Jr., Science 2009

Rabinovici et al., Annals Neurol 2008
**Tau-Immunopositive Inclusions**

- **PSP**: Globose tangle
- **Pick's Disease**: Pick body
- **CBD**: Coiled tangle

**Neurons**
- a. Tufted
- b. Dystrophic
- c. Plaque

**Astrocytes**
- d. Tufted
- e. Dystrophic
- f. Plaque

**Tauopathies**

- **Genetics of FTDs**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Familial</th>
<th>Gene</th>
<th>Tau Path</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pick's Disease</td>
<td>Sometimes</td>
<td>Chr-17 (Tau)</td>
<td>3R</td>
</tr>
<tr>
<td>FTDP-17</td>
<td>Yes</td>
<td>Chr 17 (Tau)</td>
<td>Usually 4R</td>
</tr>
<tr>
<td>CBD/PSP</td>
<td>Sometimes</td>
<td>Chr 17 (Tau)</td>
<td>4R (Tau)</td>
</tr>
</tbody>
</table>

**Some FTDP-17 mutations**
- G272V
- N279K
- R406W
- V337M
- P301L

**Ubiquitin +ve FTD (FTD-MND)**

- Dentate stained for ubiquitin

**Frontotemporal lobar degeneration: TDP-43**

- Ubiquitin-positive, TDP-43 positive

- Inclusions in sporadic ALS

- Neumann, Science 2006
**FUS/TLS (Fused in Sarcoma, Translated in Liposarcoma)**

- RNA binding protein (similar function to TDP43)
- Cause 5-15% of familial ALS
- FUS protein accounts for most ubiquitin-positive but tau and TDP43-negative FTD (5%)
- FTD cases < 40, disinhibited, caudate atrophy, sparing dorsolateral frontal region
- 5% of FTD

**Disinhibition**

**FTD Genetics**

- Genetic (40%) sporadic (60%)
  - Predominantly FTD, CBD or PSP
    - Chromosome 17 Tau - exon or intron mutations lead to abnormal tau aggregates
    - Chromosome 17 Progranulin - nonsense mutations with nuclear TDP-43 aggregates (loss of function)
  - ALS and FTD
    - Chromosome 1 - TDP-43 mutations (uncommon)
    - Chromosome 9 - Still undetermined (but close!)
    - Chromosome 16 – FUS
Progranulin Gene Structure

- 593 amino acid (68.5 kilodaltons) cysteine-rich secreted molecule
- 7.5 tandem “granulin” repeats each forming a stacked β-hairpin structure similar to EGF

Progranulin Mutations and Haploinsufficiency

- 66 mutations in progranulin, most insert premature termination codon disrupt initiator codon gene
- mRNAs with premature termination codons degraded quickly causing a complete loss-of-function
- Dominant inheritance mediated through a loss-of-function mechanism, or haploinsufficiency, is rarely seen in human genetics

Consortium to Cure FTD

- PGRN conditional mouse (Bob Farese)
  - Behavior (Lennart Mucke, Erik Roberson UAB)
- PGRN & granulin pathways, meds (Li Gan)
- PGRN worm (Aimee Kao), Neuronal cell model TDP43 Sami Barmada
- Clinic/pathology (gene carriers) (Seeley & Miller)
  - Early detection - clinical, fMRI
  - Skin cell to iPs to neuron (Farese, Fen Biao-Gao)
- PGRN Genetics
  - mRNA expression & PGRN ELISA (Dan Geschwind, Giovanni Coppola UCLA, Rosa Rademakers Mayo)

Plasma GRN Levels

Finch, Brain 2009
• Differentiation of FTD Patient-Specific iPSCells into Postmitotic Human Neurons

- Human neurons with the PGRN 116X mutation
- TUJ1 and MAP2-positive, GFAP-negative

CBD: Europe

- Delay, Brion, Escourolle -1957
  - Separate Pick’s from AD
  - Pick’ is a frontal/basal ganglia disorder with or without neuronal inclusions
- Constantinidis 1974
  - Pick’s disease type 2
  - Less severely disinhibited
  - More basal ganglia abnormalities
  - Neuronal achromasia identical to pattern described by Rebeiz

CBD: Rebeiz et al. 1968

- “corticodentatonigral degeneration + neuronal achromasia”: clin-path features 3 patients “novel” neurodegenerative condition.
- “Severe impairment control movement, abnormalities posture and involuntary motor activity. Despite serious disability, little muscular weakness, and mental faculties relatively spared till the end.”
CBD - Tau Staining in Neurons

Feany and Dickson 1996

CBD Astrocytic Plaques

Feany and Dickson 1996

Two Descriptions: Same Disease

- European: Behavioral disorder with frontal involvement
- United States: Movement disorder with sparing of cognition (prominent limb apraxia)

CBD: A Movement/Parietal Perspective

- Gibb et al 1989, Riley Lang 1990
- “cortical sensory loss, focal reflex myoclonus, alien limb phenomena, apraxia, rigidity and akinesia, a postural-action tremor, limb dystonia, hyperreflexia, and postural instability.” Asymmetry of signs and visuospatial deficits
The Evolving Story of CBD

- Rigid Parkinsonian syndrome
  - Rigid without tremor
  - Myoclonus
  - Dystonia
  - Alien limb
- Asymmetric
- Apraxic Syndrome
  - Limb apraxia
  - Visuospatial deficits

CBD After Tau

- CBD inclusions are tau positive
- CBD and PSP associated with H1 haplotype (94%)
- Tau mutations can cause CBD
- PNFA is often CBD
- bvFTD can be CBD
- Called PSP often CBD

UCSF Path Proven CBD

- 17 cases
  - bvFTD – 5
  - PNFA – 5
  - Executive Motor – 6
  - Posterior Cortical Atrophy 1
- Only 7/17 movement changes first 4 years
- 13/17 executive or language deficits vs. 4/17 early parietal deficits
- Alien foot more common than limb apraxia
- CBD fits better early European model, Pick’s variant
Path-proven Corticobasal Degeneration

- Clinical syndrome: bvFTD, Exec-Motor, PNFA

Methods
- Inclusion criteria
  - Possible or probable UCSF CBS criteria at first presentation
  - Pathological studies or PiB imaging
- Compare CBS-AD (PiB +) vs. CBS non-AD (PiB -)
- Blinded chart review
  - Symptoms
  - Signs
- Neuropsychological testing
- Voxel-based morphometry

Probable/Possible CBS
- Progressive course
- R rigidity (any one below)
  - Cogwheel rigidity
  - Non-specific limb rigidity (other than paratonia)
  - Axial rigidity
- Asymmetric cortical signs (any below)
  - Language or cortical speech deficit
  - Visual-spatial deficit with hemineglect
  - Limb apraxia

Possible, Asymmetric Cortical
- Meets progressive course and asymmetric cortical signs for possible CBD without rigidity

CBS-AD < NC and CBS-other < NC
- p(FWE<0.05)
**Take Home Message**

- Beware CBS: Often a variant of AD
  - More dorsal, basal ganglia
- CBD best predicted by dorsal and medial frontal and caudate anatomy
- Syndromes are PNFA, bvFTD (apathy > disinhibition), Exec-motor (leg)
- Is CBD asymmetric?
- Can (should) we separate CBD/PSP?

**Treatment in FTD**

- Hyperorality, carbohydrate craving, compulsions, irritability, depression may be due to low serotonin. SSRIs, SNRIs
- Memantine may have behavioral effect
- Avoid typical and atypical antipsychotics, cholinesterase inhibitors
- Work on environment with family
- Family is often disrupted prior to diagnosis

**Future Therapies**

- Anti-tau
  - Allon-208
  - Rember
- PGRN
  - Replace (medically, surgically)
  - Override nonsense mutations
  - Stimulate normal chromosome to produce more PGRN

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**Miller et al. Dementia. 1995;6:195-199.**
Progranulin

Mackenzie 2006

A

B

C

D