An Update on Frontotemporal Dementia and Other Non-AD Dementias

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Dementia with Abnormal Movement
- Idiopathic Parkinson’s Disease (PD)
- Parkinson’s Disease Dementia (PDD)
- Dementia with Lewy bodies (DLB)
- Parkinsonism in Alzheimer’s Disease
- Pure AD without Parkinsonism
- Progressive supranuclear palsy
- Corticobasal degeneration
- Prion disorders

Mixed Pathology
- AD patients show Lewy body pathology
  - Tsuang 2006 (52.6% AD show Lewy body pathology)
  - Leverenz 2006 (96% PS1 Lewy body amygdala)
- PDD and DLB patients have AD pathology
  - Ballard 2006 - 2/3 DLB Braak 5-6
  - 14-22% PD Braak 5-6
  - PDD 3-fold lower plaque vs DLB, 20% less synuclein, but 30% greater loss ChAT

Pathology

<table>
<thead>
<tr>
<th>Table 1: Relationship between pathology and duration of PD prior to dementia</th>
<th>plaque</th>
<th>Braak stage</th>
<th>Lewy body amygdala</th>
<th>ChAT loss %</th>
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<tbody>
<tr>
<td>PD 5-9 years prior to dementia (n=30)</td>
<td>7.8 (9.5)</td>
<td>2-5</td>
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75 yo male with history of visual hallucinations that progressed to severe dementia.
Dx: Mixed Alzheimer’s disease and Lewy body pathology

Substantia nigra

Bielschowsky

Entorhinal Cortex

Synuclein

PDD 3-fold less plaque VS DLB, 20% less α-synuclein pathology, but 30% greater loss ChAT

Ballard et al. (2006)
**DIAGNOSTIC CRITERIA**

1. **Dementia** (Cognitive & functional impairment)
2. **Core features:**
   - Fluctuations alertness/awareness
   - Recurrent visual hallucinations, well-formed detailed
   - Parkinsonian symptoms (e.g., axial rigidity, bradykinesia)
3. **Suggestive features** (1 sugg. + 1 core = probable; 1+ sugg. = possible):
   - REM-Behavior Disorder (RBD)
   - Neuroleptic sensitivity
   - Low DA transporter uptake SPECT/PET

**Prevalence of Dementia in PD**

- Janvin 2005 J Geriatr Psych Neurol
  - 76 non-demented PD patients over 4 years
  - Twenty-five (42%) new dementia cases
  - Poor at Stroop predicted dementia

- Janvin 2006 Mov Dis
  - 72 PD patients (34 normal, 38 MCI)
  - 4 years 62% MCI and 20% PD demented

**Cognitive Impairment in PD**

- 10% PD develop dementia over 3.5 years, 57% showed signs of cognitive impairment (largely executive control)
- *Predictors of cognitive decline:* baseline deficits in semantic fluency and pentagon copy and non-tremor dominant motor phenotype.
- Deficits related to posterior cortex (e.g., semantic fluency and pentagon copy) likely reflect cortical Lewy body pathology.

**65 y.o. surgeon with MCI-DLB**

- Copy
- Recall

**MT - Neuropsych**

- Copy
- Recall
**ET - Neuropsych**

**Hallucinations & Illusion in DLB/PDD**

**FLUCTUATIONS in DLB**
- 200 Normals, 70 DLB, 70 AD patients
- Distinguishing features suggestive of DLB:
  - daytime drowsiness and lethargy
  - daytime sleep lasting at least 2 hours
  - staring into space for long periods
  - episodes of disorganized speech
- 63% of DLB patients had 3/4 symptoms vs. 12% of AD patients = 83% pos. pred. value

**DLB/ PDD Lapses**
- Lapses awareness (e.g., “detaches”, “off with pixies”, “stops talking mid-conversation”) then returns
- No discernable trigger
- Confusion delusional/confabulatory quality (e.g., “one day says she’s been to NY, next day lucid,” “some days thinks there are extra people for dinner”, “wife is not wife” or “home is not home”)
- Degree of variation in awareness is extreme (e.g., some days can do checkbook vs. other days can not stay awake or hold conversation)

**REM Sleep Behavior Disorder**
- Parasomnia with complex motor activity in REM (e.g., kick, scream, act out dream)
- Predominantly men, mean age 50-65
- Frequently synucleinopathies (PD, PDD, MSA, DLB)
- Associated with LB pathology in brainstem
- May occur 10+ years prior to onset of a diagnosable clinical disorder (along with anosmia...earliest signs?)
- 65% RBD patients develop parkinsonian disorder

**MOTOR DYSFUNCTION**
- Tremor (postural, symmetric)
- Bradykinesia
- Rigidity (axial)
- Parkinsonian gait (stooped, shuffling)
- Decreased fine motor skills
- Masked facies
**Autonomic Dysfunction**
- Orthostatic hypotension
- Impotence
- Urinary incontinence
- Constipation

**Why Cog/Behavioral Changes**
- Neurochemical
  - Cholinergic
  - Serotonergic
  - Dopaminergic
- Protein Aggregation
  - Aβ42
  - α-synuclein
  - Tau
- Circuit Degeneration
  - Ventral Stream
  - Frontal Subcortical Circuits
  - Locus coeruleus/brainstem

**Prevalence**
- Unknown (Lund, Manchester 16%)
- Common cause pre-senile dementia
  - Ratnavalli 1:1 with AD 45-64 years (Neurology 2002)
  - Knopman more common than AD below 60 years (Neurology 2004)
  - Broader spectrum even more common (PSP, CBD, ALS)
- Less common after 70?

**Clinical Heterogeneity**
- Progressive frontotemporal dementia
- Genetic (40%) sporadic (60%)
- Frontal, temporal, left or right predominance of degeneration
- Motor overlap with PSP, CBD, ALS

**Is FTD Genetic?**
- Chromosome 17
  - Tau – exon & intron mutations
  - Progranulin mutations
- Chromosome 9 FTD-ALS (almost always Ubiquitin-TDP-43)
  - Gene or genes remain to be discovered
Frontotemporal dementia: pathology & genes

- **Tau-positive**
- **Ubiquitin-TDP-43-positive, Tau-negative**

**Chromosome 17q21:**
- MAP-T: Microtubule stability and axoplasmic transport
- PRGN: Cell proliferation and repair

Hutton, Nature 1999
Baker, Nature 2006
Cruts, Nature 2006
Neumann, Science 2006

FTD Pathological Syndrome

- **Core features**
  - Frontotemporal predominance
  - Gliosis, spongiosus, neuronal loss

- **Variable histological features**
  - Neuronal inclusions tau+ve
  - Neuronal inclusions with ubiquitin-TDP-43
  - Hippocampal sclerosis (Hatanpaa, Blass)

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### Tau-Immunopositive Inclusions

- **PSP**
  - Globose tangle

- **Pick’s Disease**
  - Pick body

- **CBD**
  - Coiled tangle

- **Neurons**
  - Tufted

- **Astrocytes**
  - Dystrophic

- **Plaque**

### Tauopathies

**Genetics of FTDs**

<table>
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<tr>
<th>Disease</th>
<th>Familial</th>
<th>Gene</th>
<th>Tau Path</th>
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<tr>
<td>Pick’s</td>
<td>Yes</td>
<td>Chr-17 (Tau)</td>
<td>3R</td>
</tr>
<tr>
<td>FTDP-17</td>
<td>Yes</td>
<td>Chr-17 (Tau)</td>
<td>4R</td>
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- 3R
- 4R
- 441
- 410

Some FTDP-17 mutations
- G272V
- N279K
- P301L
- V34F
- M1
- R406W

Hutton et al 1998

### Frontotemporal lobar degeneration: TDP-43

- **Ubiquitin-positive, TDP-43 positive**

Inclusions in sporadic ALS
Neumann, Science 2006

### Progranulin: A New FTD Gene

- Hutton, Van Broeckhoven mutations in FTD families linked to 17q21 with no Tau mutations (Baker et al. 2006; Cruts et al. 2006, Nature)
- 5-10% all FTLD cases, 23% familial cases at Mayo Clinics (Gass 2006)
- 24% cases PA (PNFA, or SD) presentation, others FTD, CBD, Parkinsonian, AD
- Family members same mutation have different phenotypes (FTD vs. PNFA) (Snowden 2006)
**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 - Haploinsufficiency**
- 43 mutations, premature termination of codon or disrupt gene initiator codon
- mRNAs with premature termination codons degraded causing complete loss-of-function (disappearance progranulin)
- Dominant inheritance mediated through a “loss-of-function”, “haploinsufficiency” rarely seen human genetics
- Progranulin growth, inflammation

**FTD: From Syndrome to Circuit to Cell & Molecules**
- The syndrome
  - Disinhibition, addictive behavior, apathy, altered social regulation & personality

**FTD: Syndrome to Region**
- Syndrome: Disinhibition, addictive behavior, apathy, altered social regulation
- Region: Ventromedial, insula, anterior cingulate, ventral striatum

**FTD: From Region to Circuit**
- Syndrome: Disinhibition, addictive behavior, apathy, altered social regulation
- Regional degeneration: Ventromedial prefrontal cortex, insula, anterior cingulate, ventral striatum
- Circuit: Frontotemporal limbic/paralimbic

**FTD: Syndrome to Circuit to Cell & Molecule**
- Syndrome: Disinhibition, addictive behavior, apathy, altered social regulation
- Regional degeneration: Ventromedial prefrontal cortex, insula, anterior cingulate, ventral striatum
- Circuit: Frontotemporal limbic/paralimbic
- Cells, Molecules, Genes
  - Von Economo Neuron, tau, progranulin, TDP-43
Early FTD

- Early symptomatic N = 15
- Symptomatic N = 15
- Severe dementia N = 15

FTD atrophy by clinical stage

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Right Posterior Cortex is Hypermetabolic and Thicker than Matched Controls

Connectivity Networks

Courtesy of Bill Seeley

Amyloid Imaging

- AD
- FTLD

Pharmacological Intervention

- Correctly identify target symptoms
- Review patient’s medical history
- Review drug’s profile / drug:drug intx
- Start with low doses
- Increase slowly
- Change one drug at a time
- Educate caregivers
- Monitor response and side-effects
- Re-evaluate need for drug
**Treatment in FTD**

- Carbohydrate craving, overeating, compulsions, irritability, depression due to low serotonin? Consider SSRI
- Consider NMDA-antagonist
- Avoid typical and atypical antipsychotics
- Avoid cholinesterase inhibitors
- Work on environment with family
- Family often disrupted prior to diagnosis

**Conclusions**

- FTD is a slow degenerative disorder
- Begins orbitofrontal, anterior cingulate, frontoinsular region (circuit), right > left
- VENs selectively vulnerable
- Opportunity to understand dysfunction of these regions, cells in humans
- Treatment is feasible!

**Progranlin (PGRN)**

Screening for mutations done by direct sequencing all 12 coding exons, non-coding exon 0, core promoter region, and entire 3' untranslated region (UTR) of the gene.

**Anatomy of Visual Hallucinations**

- Anterior ventral – landscape, figures in hats
- Superior temporal - disembodied faces with exaggerated teeth
- Dorsal stream – palinopsia

Santhouse et al. Brain October 2000