Differential Diagnosis of Young Onset Dementia: Frontotemporal Dementia

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FTD History - Pathology

- 1892 - Arnold Pick describes patient with behavior and language disturbance
- Autopsy: Diffuse temporal atrophy

FTD History - Pathology

- 1911 Alzheimer described argyrophilic inclusions (Pick bodies) and swollen achromatic cells (Pick cells).
- 1922 Gans & 1926 Onari and Spatz introduced term "Pick's Disease"

FTD History - Diagnostic Criteria

- 1994 Lund - Manchester Criteria
  - Loss of personal and social awareness
  - Disinhibition
  - Mental rigidity / inflexibility
  - Distractibility / impulsivity
  - Hyperorality
  - Perseverative / stereotyped behavior
  - Emotional unconcern
  - Progressive reduction of speech
  - Preservation of spatial orientation and praxis

Aphasic Syndromes - History

- 1982 Mesulam - Primary Progressive Aphasia (PPA)
  - Fluent: empty fluent speech, anomia, loss of word meaning (Snowden, et al 1989)

Frontotemporal Lobar Degeneration (FTLD) - History

- 1998 Neary, et. al. Frontotemporal Lobar Degeneration (FTLD)
  - 3 Clinical Syndromes:
    - Frontotemporal Dementia (FTD)
    - Progressive Non-Fluent Aphasia (PNFA)
    - Semantic Dementia (SD)
FTD Spectrum - Prevalence

- Common cause of pre-senile dementias
  15 per 100,000 in population 45-64 (Rosso, et al, 2003; Ratnavalli, et al., 2002)
- Less common after age of 70?

Frontotemporal Degenerations: Pathology

- FTLD-tau
  - PID
  - PSP
  - CBD
  - AGD
  - MSTD
  - NFT-dem
- FTLD-TDP
  - (types 1-4)
- FTLD-FUS
  - aFTLD-U
  - NIFID
  - BIBD


Frontotemporal Degenerations: Genetics

- Tau +
  - [Chromosome 17: MAPT]
- Tau -
  - [Chromosome 17: GRN]
  - [Chromosome 1: TARDP]
  - [Chromosome 9: VCP]
  - [Chromosome 9: FTD/ALS]
  - [Chromosome 3: CHMP2B]

Chromosome 17: MAPT
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Chromosome 9: FTD/ALS
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Frontotemporal Degenerations: Genetics

FTD by Syndrome

3 centers (N=353)


Frontotemporal Dementia - Anatomy

Behavioral Variant Frontotemporal Dementia (bvFTD)

Courtesy John Q. Trojanowski MD, PhD
Orbitofrontal cortex (inhibition)

Anterior cingulate (drive)

Dorsolateral prefrontal cortex (neuropsychology)

Disinhibition

BvFTD - Behavior

Patient Video

Courtesy of Murray Grossman

bvFTD - Atrophy by Severity


Disinhibition

Patient Video

Courtesy of Murray Grossman
Apathy / Inertia

Loss of empathy

Loss of Sympathy or Empathy

Simple Compulsive Behavior
Perseverative / Compulsive Behavior (speech)

Patient Video

Courtesy of Murray Grossman

Hyperorality

Patient Video

Courtesy of Murray Grossman

Hyperorality

Patient Video

Courtesy of Murray Grossman

BvFTD - Neuropsychology

Neuropsychology in Dementia

- Neuropsychological profile
- Chronology of deficits

Cognitive Profiles: FTD vs. AD

Mancova
Cov: Age, MMSE, Educ
Test * DX  F=5.46, p < .01

Correct classification: FTD = 76.9% AD = 90.9%, overall = 85.7%
Rascovar, et al., Neurology, 2002

Qualitative errors
Environmental dependence

Patient Video

Neuropsychology of bvFTD - Summary
• Generation deficits (verbal and non-verbal fluency)
• Relative preservation of memory (particularly non-verbal)
• Relative preservation of visuospatial /constructional abilities
• Errors - repetitions and rule violations
• Environmental dependency (stimulus-bound)

BvFTD - Diagnosis
### Diagnostic hierarchy for FTDC criteria

<table>
<thead>
<tr>
<th>Level of Certainty</th>
<th>Description</th>
<th>Syndrome</th>
<th>Anatomy</th>
<th>Pathology</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low / Medium high sensitivity for mild cases</td>
<td>Possible bvFTD</td>
<td>Syndrome</td>
<td>Anatomy</td>
<td>Pathology</td>
<td>Genetics</td>
</tr>
<tr>
<td>High research and clinical trials</td>
<td>Probable bvFTD</td>
<td>Syndrome</td>
<td>Anatomy</td>
<td>Pathology</td>
<td>Genetics</td>
</tr>
<tr>
<td>Certain retrospective path studies</td>
<td>bvFTD with Definite FTLD pathology</td>
<td>Syndrome</td>
<td>Anatomy</td>
<td>Pathology</td>
<td>Genetics</td>
</tr>
</tbody>
</table>

### International Consensus Criteria for bvFTD (FTDC)

#### I. Neurodegenerative Disease
- A. Shows progressive deterioration of behavior or cognition

#### II. Possible bvFTD (3 of 6)
- A. Early behavioral disinhibition
- B. Early apathy or inertia
- C. Early loss of sympathy or empathy
- D. Early perseverative, stereotyped or compulsive/ritualistic behavior
- E. Hyperorality and dietary changes
- F. Neuropsychological profile: executive deficits, relative sparing of memory and visuospatial functions

#### III. Probable bvFTD (all must be present):
- A. Meets criteria for Possible bvFTD
- B. Exhibits significant functional decline
- C. Imaging results consistent with bvFTD

#### IV. bvFTD with Definite FTLD Pathology (either B or C must be present):
- A. Meets criteria for Possible or Probable bvFTD
- B. Exhibits significant functional decline
- C. Imaging results consistent with bvFTD

#### V. Exclusion Criteria for bvFTD
- A. Pattern of deficits better accounted for by other non-degenerative nervous system or medical disorder
- B. Behavioral disturbance better accounted for by a psychiatric diagnosis
- C. Biomarkers strongly indicative of AD or other neurodegenerative process (exclusion for Probable bvFTD)

### Results:

#### Sensitivity of bvFTD criteria (common sample)

- Possible bvFTD vs. 1998 criteria: McNemar's $X^2 = 44.08, p<0.0001$
- Probable bvFTD vs. 1998 criteria: McNemar's $X^2 = 18.75, p<0.0001$

#### Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia

- Sensitivity and specificity for the Frontotemporal Dementia Consensus criteria for probable and possible behavioral variant frontotemporal dementia (bvFTD) are shown in Figure 2.

#### Figure 2

- Sensitivity: 81%
- Specificity: 91%
- Positive predictive value: 92%
- Negative predictive value: 86%
bvFTD - Caregivers

- Special considerations:
- Age of caregivers
- Psychological impact
- Loss of employment / finances
- Legal issues
- Institutionalization
- Genetic counseling

Thank you!
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FTDC

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