WHAT IF IT’S NOT ALZHEIMER’S DISEASE

Murray Grossman
Department of Neurology
University of Pennsylvania School of Medicine
• What is dementia?
  – Neurodegenerative condition that causes cognitive and social decline from adult level of competence
• Alzheimer’s disease is the most common dementia or neurodegenerative condition
  – Problems with memory and other areas that interfere with daily functioning
• What if it’s not Alzheimer’s disease?
FREQUENCY OF DEMENTIA

Alzheimer's Disease
• Plan of talk
  – Characteristics of the second most common neurodegenerative condition
  – Recent scientific findings
  – Treatment options
FRONTOTEMPORAL LOBAR DEGENERATION

- Mean age of onset 59 yrs
  - Range 30 to 82 years
- Almost as common as AD under 65 years of age
- 2 hemispheres, 4 lobes
Two major phenotypes

- Disorder of social comportment and executive functioning (55%)
- Progressive non-fluent aphasia and semantic dementia (45%)
DISORDER OF SOCIAL COMPORTEMENT

- Poor self-regulation, impulsive, disinhibited, impaired social conduct, insensitive, agitated
  - hyperoral
  - hypersexual
  - hypervisual
  - unprovoked rage
- Rigid, obsessive
- Apathetic, unmotivated
- Disinhibition and apathy are the most disturbing features for caregivers

Massimo et al, 2009
SOCIAL AND EXECUTIVE DISORDER IN FTD

- Impairment of social judgment

What will happen next?

![Diagram](image)

![Brain Scan](image)

Eslinger et al, 2007
• Limited insight into self

• Self-caregiver discrepancy on Brock Social Scale
  – SOC/EXEC patients overestimate their performance in several domains
  – SOC/EXEC overestimation much more prominent than other FTD patients

Eslinger et al, 2006
• Treatment options
  – Medications
    • Atypical neuroleptics
    • Anti-convulsants
    • Anti-depressants
  – Treatment trials now at Penn
  – Behavioral management
    • Structured environment
    • Curriculum of activities
    • Avoid exposure to provocative agents
• Progressive non-fluent aphasia

• Grammatical deficit in non-fluent speech related to left frontal atrophy

Gunawardena et al, 2010

Ash et al, 2009
LANGUAGE DISORDER IN PNFA

- Speech errors in progressive non-fluent aphasia

![Graph showing speech errors in PNFA]
FRONTOTEMPORAL DEGENERATION

Courtesy John Q. Trojanowski MD, PhD
• PNFA often due to tauopathy such as dementia with Pick bodies or corticobasal degeneration
SEMANTIC DEMENTIA

• Expression
  – Fluent but empty speech
  – Impaired confrontation naming

• Comprehension
  – Impaired word meaning
  – Impaired object knowledge

Grossman et al, 2004
Bonner et al, 2009

Weinstein et al, in press
SEMANTIC MEMORY IN SEMANTIC DEMENTIA

• Degraded representation of long-term knowledge
  – Semantic errors drawing objects
  – Poor color knowledge of objects
  – Difficulty using objects
  – Degraded auditory knowledge of objects

Lambon Ralph et al, 2001
SEMANTIC MEMORY IN SEMANTIC DEMENTIA

- Degraded object knowledge in SD
  - Reversal of the concreteness effect
  - Relatively preserved abstract concepts

Controls
Semantic dementia

Bonner et al, 2009
SEMANTIC DEMENTIA

• Preserved number knowledge

\[
\begin{align*}
2 + 3 &= 5 \\
5 + 9 &= 14 \\
12 + 13 &= 25 \\
19 + 7 &= 26 \\
28 + 35 &= 63
\end{align*}
\]

Weinstein et al, in press
SEMANTIC DEMENTIA

- Examples of embellishments in Minuet #3 in F, J. S. Bach

As Written

As Played

- Novel embellishments when re-played one month later
- Preserved knowledge of musical concepts
What is the cause of semantic dementia?

Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Manuela Neumann,1,11* Deepak M. Sampathu,1* Linda K. Kwong,5* Adam C. Truax,1 Matthew C. Micsenyi,1 Thomas T. Chou,6 Jennifer Bruce,5 Theresa Schuck,1 Murray Christopher M. Clark,3,4 Leo F. McCluskey,3 Bruce L. Miller,6 Eliezer Masliah,7 Ian R. Mackenzie,8 Howard Feldman,9 Wolfgang Feiden,10 Hans A. Kretzschmar,1 John Q. Trojanowski,1,4,5 Virginia M.-Y. Lee5,4,5*†

TDP-43 is a nuclear protein important for DNA transcription and repair

Neumann et al, 2006
• Autopsy shows left temporal atrophy
• Surface layer neuronal dropout
• Ubiquitin and TDP-43 immunoreactive neuronal inclusions
• **Treatment options**
  
  – **Medications**
    • Dopaminergic supplementation
    • Cholinesterase inhibitors
  
  – **Treatment trials at Penn**
  
  – **Behavioral management**
    • Speak slowly
    • Use multiple modalities (e.g. gesture)
    • Speak redundantly
    • Personalized picture dictionary
    • Use simple sentence structures
    • Small group conversations
ALS is a TDP-43 proteinopathy.
WHITE MATTER DISEASE IN ALS and FTD

• MRI changes in patients with ALS-FTD

• Atrophy of cortical projection fibers using diffusion tensor imaging
Studies of families with FTLD
Basis of inherited disease defined in about 15% of FTLD
- Chromosome 17  MAPT
- Chromosome 17  GRN
- Chromosome 1  TARDBP
- Chromosome 9  VCP
- Chromosome 9  ALS/FTD
- Chromosome 3  CHMP2B

Additional 25% of FTD patients have a positive family history
- Close relative has FTD spectrum disorder
Biomarkers define pathology during life in a minimally invasive fashion.

Useful for:
- Prognosis
- Understanding disease
- Identifying candidates for etiologically-specific treatments
NOVEL TREATMENTS FOR FTD

• Several novel treatments under development
  – Trial for tauopathy beginning in October

• Who should be treated?

• How do we know if treatment works?
  – Cognitive studies of FTD
  – Imaging studies of FTD
  – Biofluid studies of FTD
• Cognitive deficit associated with specific pathology
  – Deficit persists longitudinally
IMAGING BIOMARKERS IN FTLD

• Combining grey matter with white matter imaging improves diagnostic accuracy in individual patients
  – T1 and DTI in 49 patients with autopsy or CSF diagnosis
• FTLD has frontal and anterior temporal change
• AD has medial temporal and parietal atrophy

Avants et al, 2010
• Distinguishing between FTLD-TDP and FTLD-tau
  – SVM selects imaging voxels that co-vary with multi-modal categorization model including pathology, neuropsychology, and demographic features
  – FTLD-TDP < FTLD-tau
    • GM voxels in ventral and inferior frontal, parietal, and temporal regions
    • WM voxels in dorsal cingulum
  – FTLD-tau < FTLD-TDP
    • WM voxels in uncinate and inferior frontal-occipital fasciculus
CSF BIOMARKERS IN FTD

- CSF tau is significantly lower in autopsy-proven FTD than AD
  - Tau/Abeta 42 ratio
    - FTD: 0.52
    - AD: 2.22

- Tau/Abeta 42
  - tau 403.05 pg/ml
  - Abeta 42 313.16 pg/ml

- Area Under the Curve
  - tau 78.6%
  - Abeta 42 7.8%
  - tau/Abeta 42 92.7%

- Source of the Curve
  - tau
  - Abeta 42
  - tau/Abeta 42

- Sensitivity
  - CSF TAU in over 20% of FTD patients but never low in AD patients

- Bian et al, 2008

- CSF tau is significantly low in over 20% of FTD patients but never low in AD patients
Five CSF analytes distinguish FTLD-TDP (grey) from FTLD-tau (white) in autopsy-confirmed cases of FTLD

- Diagnostic accuracy=82.6%
- Sensitivity=85.7%
- Specificity=77.8%
FRONTOTEMPORAL DEGENERATION

• Goal is find a cure in 10 years
<table>
<thead>
<tr>
<th>COLLABORATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
</tr>
<tr>
<td>Geoff Aguirre</td>
</tr>
<tr>
<td>Anjan Chatterjee</td>
</tr>
<tr>
<td>Dana Clay</td>
</tr>
<tr>
<td>Branch Coslett</td>
</tr>
<tr>
<td>Marianna Diloyan</td>
</tr>
<tr>
<td>Lauren Elman</td>
</tr>
<tr>
<td>Rachel Gross</td>
</tr>
<tr>
<td>Howard Hurting</td>
</tr>
<tr>
<td>Tsao-Wei Liang</td>
</tr>
<tr>
<td>Lauren Massimo</td>
</tr>
<tr>
<td>Leo McCluskey</td>
</tr>
<tr>
<td>Andrew Siderowf</td>
</tr>
<tr>
<td>Matt Stern</td>
</tr>
<tr>
<td>Beth Wood</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

- Generous support from NIH, and the patients and families participating in this work