Dementia for the non-expert
*The Aging Brain* June 8, 2018
Brad Dickerson, MD
MGH FTD Unit & Center for Translational Brain Mapping
Disclosures

Data Safety Monitoring Board:
  Merck

Consulting:
  Lilly, Biogen, Wave LifeSciences, Piramal
  Med Learning Group, Haymarket Media, Catamount
  Best Doctors.com, GrandRounds.com

Royalties:
  Oxford University Press (*Dementia: Comprehensive Principles and Practice*, 2014)
  Cambridge University Press (*Hodges’ Frontotemporal Dementia*, 2016)

Editorial Board:
  Neuroimage: Clinical; Cortex; Alzheimer’s & Dementia; Hippocampus;
  Neurodegenerative Disease Management
Objectives

Summarize recent advances in the diagnosis of neurodegenerative dementias.

Review atypical forms of Alzheimer’s disease and related disorders.

Examine the value of earlier diagnosis on treatment and care of patients and families with neurodegenerative dementias.
Neurodegenerative Diseases:
The traditional approach through clinical diagnosis

- Alzheimer’s disease (diagnosed after dementia)
- frontotemporal dementia (FTD)
  - behavioral variant (“Pick’s disease”)
  - primary progressive aphasias
- posterior cortical atrophy (PCA)
- progressive supranuclear palsy (PSP)
- corticobasal degeneration (CBD)
- dementia with Lewy bodies (DLB)
- Huntington’s disease
- Parkinson’s disease
- ALS (Lou Gehrig’s disease)

Predominantly cognitive / behavioral symptoms
 Predominantly motor symptoms
 Cognitive / behavioral & motor symptoms
Patients with clinical AD dementia were enrolled.

Anti-amyloid trial failed to show clinical benefit.

About 17% of cohort were found not to have amyloid in the brain.
Clinico-pathological overlap

78 y woman with gradually progressive memory loss, loss of ability to problem-solve, lack of initiation of tasks, required support from husband to manage activities
  clinical diagnosis probable mild AD dementia
    --biomarkers not consistent with AD

62 y man with gradually progressive executive dysfunction and reduced speech with relative sparing of memory; loss of interest in social activities; partial insight; fired from job; wife concerned that he is no longer able to manage affairs independently
  clinical diagnosis probable Frontotemporal Dementia
    --biomarkers consistent with AD
The continuum of neurodegenerative dementias

Cognitive & Other Functions

Preclinical

Prodromal/MCI

Dementia

Biomarkers consistent with ADRD pathology

Accumulating pathology

Disease Progression

Mild, moderate, severe
Objectives

Summarize recent advances in the diagnosis of neurodegenerative dementias.

Review atypical forms of Alzheimer’s disease and related disorders.

Examine the value of earlier diagnosis on treatment and care of patients and families with neurodegenerative dementias.
Overall Approach To and Goals of Evaluation

• **The clinical illness**
  
  – What is the patient’s overall dementia clinical status?
    
    • Subjective cognitive concern, MCI, dementia (& dementia stage)
  
  – Is there a recognizable clinical syndrome?
    
    • Amnesic and dysexecutive dementia, aphasic MCI, etc.
  
  – Are there important accompanying clinical features?
    
    • Motor features, psychiatric symptoms, medical conditions

• **The neurobiological disease**
  
  – What laboratory, imaging, or other biomarker evidence do we have for the specific brain disease?

• **How can we use all of this information to develop a comprehensive treatment and care plan?**
Approach to diagnosis
Clinical practice

Clinical Status

Symptoms

Signs

Brain Anatomy

Brain Physiology

Brain Pathology
Approach to diagnosis
Clinical practice

Clinical Status

Symptoms
Signs

Brain Anatomy
Brain Physiology

Brain Pathology
Neurocognitive Disorders: DSM 5

• Major neurocognitive disorder (dementia)
  – Major cognitive decline (preferably by neurocognitive testing or, in its absence, other quantified clinical testing)
  – *Interferes with independence*
  – Not due to delirium
  – Not attributed to another mental disorder (eg, major depression, schizophrenia)

• Mild neurocognitive disorder (MCI)
  – Mild cognitive decline (preferably by neurocognitive testing or, in its absence, other quantified clinical testing)
  – *Does not interfere with independence*
  – Not due to delirium
  – Not attributed to another mental disorder (eg, major depression, schizophrenia)
Neurocognitive Disorders in DSM 5: Impairment Across 6 Key Domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex attention</td>
<td>Ability to attend to and process multiple stimuli</td>
</tr>
<tr>
<td>Executive function</td>
<td>Ability to plan, organize, and complete tasks/projects</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Acquiring, manipulating, and remembering items, facts, words and their meanings, events, people, procedures, skills, etc.</td>
</tr>
<tr>
<td>Perceptual-motor</td>
<td>Identification and manipulation of figures, maps and items; motor tasks; recognition of faces and colors</td>
</tr>
<tr>
<td>Language</td>
<td>Expressive and receptive language skills</td>
</tr>
<tr>
<td>Social cognition</td>
<td>Socially appropriate behaviors and decision-making; empathy</td>
</tr>
</tbody>
</table>
Major cortical brain networks
“Typical” MCI / prodromal AD

• 72 year old man, retired tax attorney
• Gradually increasing forgetfulness over past 2 years
  • Did not remember the “whole evening” of Superbowl party the next week; frequently argues with family about memory lapses
• Does family taxes but takes longer, serves on local housing community board, plays golf
• Wife/daughter prompted clinic visit

• Office visit & neuropsychological testing revealed poor learning of word list (5-7-8-9-10), difficulty with free recall (4), relatively preserved recognition (13/16 with 2 false positives); otherwise intact
Atrophy in multiple cortical networks in typical mild AD dementia

Dickerson BC, et al., Cerebral Cortex, 2009
Major clinical phenotypes of AD

a. **Memory**: (most common; referred to as typical): The deficits should include impairment in learning and recall of recently learned information along with deficits in other cognitive domains

b. **Language**: The most prominent deficits are in word-finding; deficits in other cognitive domains should be present (Primary progressive aphasia)

c. **Visuospatial**: The most prominent deficits are in spatial orientation, visual object recognition (e.g., faces), reading/writing (Posterior cortical atrophy)

d. **Executive function**: The most prominent deficits are impaired reasoning, judgment, and problem solving

e. **Personality (social-emotional)**: Frontal variant AD

f. **Motor**: (Corticobasal syndrome)
   a. Atypical are much more common in young-onset (<65)
Primary Progressive Aphasia (“logopenic”)

- Retired engineer who presented to the MGH FTD unit at 70 with 4 year history of progressive language and word-finding difficulties
- 4 years prior, he and his wife began to observe word-finding pauses and sound substitutions
- More difficulty ‘getting words out’, increased use of word substitution and ‘talking around things’
- Difficulty naming common objects; could think of the object and describe it, but was unable to name it
- Patient noted decline in sustained attention but denied difficulties with memory, comprehension, visuospatial skills, executive function, math skills
- Very independent in daily function
Primary Progressive Aphasia ("logopenic")
Language Samples

Age 70

• Looks like a family is uh has a hou- uh I think it’s a house or a friend’s place on the leck-lake. And the kids are having a good time. They’re gonna have a picnic. Uh, and uh they have somebody who is uh finishing-fishing. The kids are playing, uh, uh one is working uh is playing the girls, playing with-with uh uh putting together a sand castle. Uh the boy is- uh has a uh kite. Uh some friends are in the boat, in the so-saiboat-sail-sailboat. And they- I think they are sort of waking...the wave.

Age 75-76

• Minimal intelligible content due to high frequency of phonemic parahasias and neologisms, occasional short phrases are recognizable

• By age 76, fewer recognizable words/phrases
Age 70

RIGHT

Age 75

LEFT
Diagnostic Criteria: PPA

– PPA Dx requires 3 features to be present
  • most prominent clinical feature is difficulty with language
  • language deficits are the principal cause of impaired daily function
  • aphasia is most prominent deficit at symptom onset and for the initial phases of illness

– Dx requires the *absence* of 4 features
  • prominent initial episodic memory, visual memory, or visuoperceptual impairments
  • prominent initial behavioral disturbance

– May be due to FTLD or AD pathology

Gorno-Tempini et al., Neurology 2011
PPA Support Group with music therapy
Neurodegenerative Clinical Syndromes

• Labels the patient’s/family’s experience of the illness
  – (e.g., Mild amnesic and dysexecutive dementia (predominant symptoms are memory loss and executive dysfunction) with or without mood or behavioral or motor symptoms)

• Helps identify symptoms for therapy of various sorts
  – E.g., Donepezil; memory cues

• Captures some elements of care planning and support needs
  – E.g., Structured routine with care companion + education and psychosocial support for patient and care partner

• Connects them with appropriate community resources
  – E.g., Alz Assoc, Assoc for FTD, Cure PSP, Lewy Body Association, etc
Approach to diagnosis

Clinical Status

Symptoms

Signs

Brain Anatomy

Brain Physiology

Brain Pathology

The disease
The Spectrum of Diseases Causing Neurocognitive Disorders

- Alzheimer’s disease
- Cerebrovascular disease
  - Cortical
  - Subcortical
- Frontotemporal Lobar Degeneration
  - Behavioral variant
  - Semantic dementia
  - Progressive aphasia
  - Progressive supranuclear palsy
  - Corticobasal degeneration
- Lewy body disease/PD
- ALS

- Medical
  - Neoplasm
  - Trauma/anoxia
  - NPH
  - Toxins
  - Infections
  - Neurologic illness
  - Organ failure
Roles of biomarkers in dementia:
Clinical practice, 2018

Clinical Status

- Symptoms
- Signs

Brain Anatomy
- CT/MRI:
  Identification of regional atrophy

Brain Physiology
- SPECT/FDG-PET:
  Identification of regional reductions in function

Brain Pathology
- CT/MRI:
  Indicators of brain pathology
- CSF biomarkers
  Molecular imaging
FDG-PET: AD
FDG-PET: FTD
FDG-PET: AD or FTD?
FDG-PET: early stage AD?
In vivo molecular biomarkers of Alzheimer’s disease neuropathology: CSF is available, PET is research
<table>
<thead>
<tr>
<th>Neurodegenerative Clinical Syndromes</th>
<th>Neurodegenerative Pathologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnesia (memory)</td>
<td>Often but not always AD</td>
</tr>
<tr>
<td>“Typical AD”</td>
<td></td>
</tr>
<tr>
<td>Aphasia (language)</td>
<td>FTLD tau, FTLD TDP&lt;sub&gt;43&lt;/sub&gt;, AD</td>
</tr>
<tr>
<td>Primary progressive aphasia</td>
<td></td>
</tr>
<tr>
<td>Vision</td>
<td>Usually AD</td>
</tr>
<tr>
<td>Posterior cortical atrophy</td>
<td></td>
</tr>
<tr>
<td>Social-emotional behavior</td>
<td>Usually FTLD tau or TDP&lt;sub&gt;43&lt;/sub&gt;</td>
</tr>
<tr>
<td>Behavioral variant FTD</td>
<td></td>
</tr>
<tr>
<td>progressive supranuclear palsy (PSP)</td>
<td>FTLD tau</td>
</tr>
<tr>
<td>corticobasal degeneration (CBS)</td>
<td>Usually FTLD tau, AD</td>
</tr>
<tr>
<td>dementia with Lewy bodies (DLB)</td>
<td>alpha synuclein</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>alpha synuclein</td>
</tr>
<tr>
<td>ALS (Lou Gehrig’s disease)</td>
<td>ALS TDP&lt;sub&gt;43&lt;/sub&gt;</td>
</tr>
</tbody>
</table>
Patient with progressive visual symptoms: MRI with subtle shrinkage

Diagnosis: MCI with the Posterior Cortical Atrophy syndrome (Crutch S et al., 2017)
Patient with progressive visual symptoms: FDG PET with focal hypometabolism

Diagnosis: MCI with the Posterior Cortical Atrophy syndrome (Crutch S et al., 2017)
Patient with progressive visual symptoms: “Positive amyloid PET scan”

Diagnosis: MCI with the Posterior Cortical Atrophy syndrome (Crutch S et al., 2017)
Patient with progressive visual symptoms: FDG PET with focal hypometabolism

Diagnosis: MCI with the Posterior Cortical Atrophy syndrome (Crutch S et al., 2017)
Patient with progressive visual symptoms: Tau PET with focal elevated signal

Diagnosis: MCI with the Posterior Cortical Atrophy syndrome (Crutch S et al., 2017)
Large-scale Language Network

Functional MRI map of the normal language network
Large-scale Language Network

Functional MRI map of the normal language network

Map of atrophy in progressive aphasia
Large-scale Language Network

- Functional MRI map of the normal language network
- Map of the location of tau pathology in the brain
- Map of atrophy in progressive aphasia
Click on this link to see the video of Carol’s journey with Frontotemporal Dementia

https://www.statnews.com/2017/03/17/dementia-frontotemporal-symptoms/
Research to improve medications to treat AD
Prior Failures with Amyloid Directed Immune Therapies

- Solanezumab, bapineuzumab, and crenezumab all failed in mild to moderate Alzheimer’s Disease
  - Not early enough
  - Did not all use amyloid PET as requirement for enrollment
  - None displayed convincing evidence that they “clear” amyloid plaques
Advances in Targeting Molecular Pathology

Sevigny et al., *Nature*, 2016
Amyloid Clearance Only Matters If It Slows or Reverses Cognitive Decline!

Sevigny et al., *Nature*, 2016
Diagnostic Criteria for AD (NIA-AA and IWG)

- **AD dementia**
  - Cognitive impairment
  - Impairment of activities of daily living
  - Biomarker evidence of AD

- **Prodromal AD (MCI of the AD type)**
  - Amnestic or non-amnestic cognitive impairment
  - No or minor impairment of activities of daily living
  - Biomarker evidence of AD

- **AD at-risk state (preclinical AD)**
  - No cognitive impairment on testing (possible subjective impairment)
  - No functional impairment
  - Biomarker evidence of AD

Emergence of Prevention Trials: A Way Forward?
Challenges of Trials and Clinical Care in Preclinical and Prodromal Disease

• What is the impact of telling people that they have “preclinical AD”
  – Including implications for insurance, employment, etc.

• What is the expense of intervening in preclinical phases?
Challenges of Trials and Eventual Clinical Care in Preclinical Disease

- Not clear what to measure to see if a drug is working when people have minimal or no symptoms
- Not clear who will develop clinical AD (do all those with positive amyloid PET scan develop symptoms?)
  - Large range of conversion (10-50%) to MCI/AD over 5-10 years in prior studies
- Expensive to obtain Amyloid PET scans for screening
  - Are there screening measures? How frequently?
- Variable time course for progression within timeframe of a study
Development of Tau Antibodies

Holztman et al., *Alz & Dementia*, 2016

Yanamandra et al., *Annals Clinical and Translational Neurology*, 2015
Need for Alternative Strategies: U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk

Does a recipe that combines lifestyle interventions prevent or delay cognitive decline in larger population?

U.S. POINTER will evaluate two lifestyle interventions

- Physical Exercise
- Nutritional Counseling & Modification
- Cognitive & Social Stimulation
- Improved Self-Management of Health Status
Targeting Diversity Recruitment in U.S. POINTER

• Recruitment process designed to increase participation of under-represented communities
• EMR search within a zip code with proximity to a YMCA and local Alzheimer’s Assoc. chapter.
  – Priority on racial, ethnic & rural populations
• Target: 23% from racial/ethnic minority groups reflecting 2016 US Census
• Target 50% women
The Importance of WW-FINGERS

- Focus on modifiable risk factors and brain health
- Dementia can potentially be reduced impacting disability
- Crucial for LMIC areas
- Global diversity
  - Ethnic differences, customs, food, culture, and attitude
- Sharing of methods and data
- Potential for FASTER dissemination/uptake to impact cognitive health
Interventions: treating pathology, symptoms, promoting resilience

- Preclinical
- Prodromal
- Dementia

Accumulating FTLD pathology
Biomarkers consistent with ADRD pathology

Cognitive/Behavioral Function
Disease Progression
Interventions: treating pathology, symptoms, promoting resilience

Cognitive/Behavioral Function

Disease Progression

Preclinical

Prodromal

Dementia

Interventions

Biomarkers consistent with ADRD pathology

Accumulating FTLD pathology
Interventions: treating pathology, symptoms, promoting resilience

Cognitive/Behavioral Function

Disease Progression

Preclinical

Prodromal

Dementia

Interventions: treating pathology, symptoms, promoting resilience

Biomarkers consistent with FTLD pathophysiology

Accumulating FTLD pathology
Interventions: treating pathology, symptoms, promoting resilience

Disease Progression

Cognitive/Behavioral Function

Preclinical

Prodromal

Dementia

Interventions

Biomarkers consistent with FTLD pathophysiology

Accumulating FTLD pathology
The MGH FTD Unit staff joins forces with pharma, advocacy groups, patients and families, and other clinicians and scientists at the Mass State House on Rare Disease Day the last day of February.
Thank you!

MGH FTD Unit & Center for Translational Brain Mapping
Affiliated with the Mass ADRC and Martinos Center for Biomedical Imaging

Thanks for funding to:

With collaborators: P50 AG005134, R01 AG045390, U54 NS092089, R01 AG048351, R01 AG038791, U01 AG052943
Dickerson PI or MPI: R01 DC014296, R01 AG056015, R01 AG054081, R01 MH113234, R21 AG056958, R56 AG057195, Alzheimer’s Drug Discovery Foundation, Krupp Foundation