Dementia: A Comprehensive Update 2016

Neuroimaging, CSF, and genetic biomarkers in dementia

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Progression of Alzheimer’s Disease: similar model for many other diseases

Accumulating pathology

Cognitive Function

Presymptomatic

Prodromal

Clinical Dementia

Mild Cognitive Impairment

Probable Alzheimer’s Disease

Disease Progression
Roles of biomarkers in dementia: Clinical practice, 2016
April 2011: New diagnostic criteria for Alzheimer’s Disease

- **Preclinical AD**
- **MCI: High likelihood AD**
- **AD Dementia**

Accumulating pathology

Cognitive Function

Biomarkers consistent with AD pathophysiology

Disease Progression

Mild Cognitive Impairment

Probable Alzheimer’s Disease
Illustrative cases

• Case 1
  • 72yo with gradually progressive impairment of memory, orientation, and judgement and problem-solving; neuropsych testing showed amnesia, executive dysfunction, and visuospatial impairment

• Case 2
  • 54yo with gradually progressive changes in judgment and decision-making, social and interpersonal behavior, and language; neuropsych testing showed executive dysfunction, anomia with sparing of memory and visuospatial function

• Case 3
  • 52yo with gradually progressive difficulties with judgement and problem-solving and high-level verbal skills, lack of insight; neuropsych testing showed executive dysfunction with sparing of memory, language, and visuospatial function
Roles of biomarkers in dementia: Clinical practice, 2016

Clinical Status

Symptoms

Brain Anatomy

Signs

Brain Physiology

Brain Pathology

CT/MRI:
Identification of brain pathology
Structural measures of pathology or abnormal neuroanatomy in dementias

• Identification of contributors to cognitive/behavioral impairment
  - A variety of types of brain pathology can cause various forms of dementia, including cerebrovascular disease, tumor, and other lesions
  - These are relatively uncommon in “typical” cases but should be surveyed

• Identification of changes consistent with neurodegeneration
  - Careful visual inspection of clinical anatomical brain MRI can reveal patterns consistent with specific neurodegenerative diseases
Cerebrovascular disease

CT  MRI-FLAIR  MRI-T2

DWMH  PVHyper

Normal Pressure Hydrocephalus

- dementia, ataxia, incontinence
- SAH/meningitis history?
- enlarged ventricles out of proportion to sulci

- relatively uncommon
- surgical management?
  - efficacy is controversial
51 y/o woman with rapidly progressive cognitive impairment and gait ataxia, developed intermittent jerking motions of both arms and legs, and expired 4 months after the first symptoms developed.
Creutzfeld-Jacob Disease

53 y/o man with rapidly progressive cognitive impairment
Roles of biomarkers in dementia: Clinical practice, 2016

Clinical Status
- Symptoms
- Signs

Brain Anatomy

Brain Physiology

Brain Pathology

CT/MRI:
Identification of regional atrophy
Alzheimer’s Disease: MTL & temporoparietal atrophy
Alzheimer’s Disease: MTL & temporoparietal atrophy
Alzheimer’s Disease: MTL & temporoparietal atrophy
FTD: Frontal & anterior temporal atrophy (spares parietal)
PPA--semantic: Left anterior temporal
PPA--nonfluent: Left frontoinsular atrophy (spares temporal)
PPA: Left anterior temporal atrophy (spares frontal)
Posterior Cortical Atrophy:
Parietal atrophy
PCA: Parietal atrophy (spares temporal)
PCA: Parietal atrophy (spares frontal)
PCA: Parietal atrophy (spares frontal)
Progressive supranuclear palsy: Midbrain atrophy

Figure 5. New radiographic sign for the diagnosis of progressive supranuclear palsy (PSP). Midsagittal MR image of a patient with Parkinson disease (PD) does not show any apparent abnormality (A), while that of a patient with PSP shows marked atrophy of midbrain tegmentum (B), and a patient with multiple-system atrophy of the Parkinson type (MSA-P) shows marked atrophy of pons (C). The midbrain to pons ratio is always small in the patients with PSP. In patients with PSP, the shapes of midbrain tegmentum (bird’s head) and pons (bird’s body) on midsagittal MR images look like a lateral view of a standing penguin (especially the king penguin) with a small head and big body. Recognition of this penguin silhouette sign should strongly raise suspicion for the diagnosis of PSP.

Oba H et al., Neurology 2005
Use of Volumetrics in the Clinic

**MORPHOMETRY RESULTS**

<table>
<thead>
<tr>
<th>Brain Structure</th>
<th>Volume (cm³)</th>
<th>% of lCV (5%-95% Normative Percentile*)</th>
<th>Normative Percentile*</th>
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<tbody>
<tr>
<td>Hippocampi</td>
<td>4.76</td>
<td>0.35 (0.41-0.56)</td>
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<tr>
<td>Lateral Ventricles</td>
<td>62.19</td>
<td>4.60 (1.89-4.78)</td>
<td>92</td>
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<tr>
<td>Inferior Lateral Ventricles</td>
<td>5.76</td>
<td>0.43 (0.15-0.32)</td>
<td>&gt; 95</td>
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</tbody>
</table>

*Charts and normative values are provided for reference purposes only. The FDA has not approved their use for diagnostic purposes.*

www.cortechslabs.com/neuroquant/
Roles of biomarkers in dementia: Clinical practice, 2016

Clinical Status

- Symptoms
- Signs

Brain Anatomy

Brain Physiology

Brain Pathology

FDG-PET/SPECT:
Identification of regional reductions in function
FDG-PET: glucose metabolism

- major use in clinical dementia:
  AD vs. FTD

Normal Aging  Alzheimer’s  FTD
Aging, MCI, AD: FDG-PET

Cognitively intact older adult

Mild Cognitive Impairment

Alzheimer’s Disease
FDG-PET: glucose metabolism: DLB, CBD

CBD
Normal temporoparietal, occipital metabolism

DLB
Temporoparietal hypometabolism, occipital hypometabolism
FDG-PET: glucose metabolism: DLB, CBD

Asymmetric perirolandic (posterior frontal, anterior parietal) hypometabolism

Temporoparietal hypometabolism, occipital hypometabolism
FDG-PET in Normal Aging, MCI, AD, and FTD

NL = normal; pAD = prodromal Alzheimer’s disease; fTD = frontotemporal dementia.
Roles of biomarkers in dementia: Clinical practice, 2016

Clinical Status

Symptoms

Brain Anatomy

Signs

Brain Physiology

Brain Pathology

SPECT/PET:
Measures of neurotransmitter system function

CSF biomarkers
(Molecular imaging)
Amyloid imaging with PET
Pittsburgh Compound-B (PIB)

Alzheimer’s disease

Normal aging
Presymptomatic Alzheimer’s Disease
Amyloid imaging with PET

55 y/o
PS1 Carrier
DM

60 y/o
Normal Control
F18 Amyloid Imaging Tracers

Flutemetamol\(^1\)  
Florbetapir\(^2\)  
Florbetaben\(^3\)  
Navidea NAV4694\(^4\)

### Amyloid Imaging Correlates With Amyloid Pathology

<table>
<thead>
<tr>
<th>F18-AV-45 PET</th>
<th>Visual Read</th>
<th>AV45 SUVr</th>
<th>Amyloid Staining (4G8 antibody)</th>
<th>Amyloid Burden (Quant IHC) (%)</th>
<th>Neuropathologic Diagnosis</th>
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<tr>
<td>MCI</td>
<td>1</td>
<td>1.08</td>
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<td>0.0</td>
<td>Normal brain</td>
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<tr>
<td>AD</td>
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<td>PDD</td>
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<td>AD with cortical Lewy bodies</td>
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<tr>
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<td>AD</td>
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<tr>
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<td>8.6</td>
<td>AD</td>
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</table>

SUVr = standard uptake value ratio; PDD = Parkinson’s disease dementia; HC = healthy control.

Interpreting Amyloid PET Scans

Figure 2. Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status

The prevalence estimates were generated from generalized estimating equations. The model included age and cognitive status as predictors. Shading indicates 95% CIs; SCI, subjective cognitive impairment; MCI, mild cognitive impairment.
Amyloid Imaging Taskforce
Appropriate-Use Criteria

Amyloid imaging is appropriate in the following situations.

1. A cognitive complaint with objectively confirmed impairment
2. Performed only after full standard workup is completed
   – Structured clinical evaluation with objective neurocognitive testing
   – Structural brain imaging
   – Relevant laboratory tests
3. AD is a possible diagnosis, but it is uncertain.
4. Knowledge of Aβ pathology would increase diagnostic certainty and alter management.
5. Should only be ordered by experts in dementia
   – Specialty training and a practice with ≥25% dementia care
   – Geriatric/behavioral psychiatry and neurology

Inappropriate Use of Amyloid PET Imaging

Amyloid PET imaging is inappropriate:

1. For evaluation of individuals without cognitive complaints; however, preclinical AD may become an indication for amyloid Imaging if preventive treatments are proved to be effective.

2. When standard recommended clinical diagnostic testing has not been ordered for initial assessment.

3. As a stand-alone diagnostic for AD dementia.

4. To assess disease progression.

Imaging Dementia—Evidence for Amyloid PET Scanning: IDEAS Study
www.ideas-study.org

- **Participants**: 18,488 Medicare beneficiaries meeting specific AUC* enrolled over 24 months at US sites as part of a CMS CED research program.

- **Aim 1**: assess impact of amyloid PET on short-term patient management.

- **Aim 2**: compare medical outcomes at 12 months for patients enrolled in the study with a matched control cohort of patients who have never undergone amyloid PET.
  
  – based on Medicare claims data imaging

*Amyloid PET should only be considered in patients with clear, measurable cognitive deficits when there is substantial diagnostic uncertainty after a comprehensive evaluation by a dementia specialist; AUC = appropriate use criteria; CMS = Centers for Medicare & Medicaid Services; CED = Coverage with Evidence Development.

**Tau PET Imaging (^{11}C-PBB3)**

Dopaminergic Function (DAT)

AD  Parkinson’s Disease  DLB
Cerebrospinal fluid markers

Alzheimer’s Disease
• Abeta 1-42 – reduced in AD
• Total-tau – elevated in AD as well as other disorders
• Phospho-tau – elevated specifically in AD

Other neurodegenerative disorders
• FTD
• DLB
Illustrative cases

• Case 1
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• Case 3
  • 52yo with gradually progressive difficulties with judgement and problem-solving and high-level verbal skills, lack of insight; neuropsych testing showed executive dysfunction with sparing of memory, language, and visuospatial function
Case 1
Illustrative cases

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CSF tau level

CSF amyloid-β level
Consistent with AD pathology

Aβ = 255; btau = 459; ptau = 77
Illustrative cases

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Case 3

FDG-PET

PiB-PET
Genetic testing

What genes?

- Early onset AD (PS1 >> PS2, APP)
- FTD (MAPT, PGRN, C9ORF, *FUS*)

Whom to test?

How to perform testing
Case example

39 y female with 2 year history of gradually progressive dementia

Predominantly executive dysfunction, lesser degree of memory impairment

Father with clinical diagnosis of Pick’s disease, onset in early 50s, died at 57, no autopsy
Relatively mild MTL atrophy

39y female
Prominent temporoparietal atrophy

39y female
Temporoparietal hypometabolism

39y female: FDG-PET
Case example

39 y female with 2 year history of gradually progressive dementia

Predominantly executive dysfunction, lesser degree of memory impairment

Father with clinical diagnosis of Pick’s disease, onset in early 50s, died at 57, no autopsy

Genetic testing revealed mutation in Presenilin 1

Autopsy (age 44) revealed AD pathology
Early onset Alzheimer’s disease patient
Age of onset < 65 years

Family hx:
Negative, no other affected family members

Low likelihood of detecting mutation, genetic testing not recommended. If patient is < 50 yrs., may want to proceed with testing

Family hx: positive with ≥ 2 other affected 1st or 2nd degree relatives with early onset disease

Access to genetic counseling with neurologist or genetic counselor with experience in neurodegenerative diseases

Counseling and clinical testing for PSEN1:
- DNA banking
- Explore autopsy to confirm diagnosis
- Refer to the Alzheimer’s Association for ongoing support

Counseling: patient and or family decline genetic testing

- Offer DNA banking
- Explore possibility of autopsy to confirm diagnosis for the family
- Refer to the Alzheimer’s Association for ongoing support

Williamson J et al., Neurologist, 2009
Roles of biomarkers in dementia evaluation: Clinical practice, 2016

• Routine MRI
  • Important first step to evaluate for various forms of pathology
• High-resolution MRI with thin coronal cuts
  • Useful for identifying specific atrophy patterns
• Functional brain studies: FDG-PET or SPECT
  • Differential diagnosis of AD vs. FTD
  • Useful for identifying many other patterns
• “In the eye of the beholder”: Look at your scans personally!
• CSF study: To evaluate for evidence of AD pathobiology
• Genetic testing: For diagnostic purposes particularly in early onset dementias
Looking ahead:
Future uses of biomarkers in neurodegenerative diseases

Early diagnosis of mildly symptomatic individuals

More confident diagnosis of atypical cases

Risk assessment in asymptomatic individuals?

Identification of candidates for clinical trials

Predicting effects of treatment

Monitoring of effects of treatment
Progression of neurodegenerative diseases

Disease Progression

Presymptomatic

Prodromal

Clinical Disease

Neurologic Function
Progression of neurodegenerative diseases

- Presymptomatic
- Prodromal
- Clinical Disease

Neurologic Function

Disease Progression

Accumulating pathology
Progression of neurodegenerative diseases

Presymptomatic

Prodromal

Regional brain volume

Clinical Disease

Disease Progression

Neurologic Function

Accumulating pathology
Progression of neurodegenerative diseases

Presymptomatic
Prodromal
Clinical Disease
Regional brain volume
Hypometabolism
Accumulating pathology
Disease Progression of neurodegenerative diseases

Accumulating pathology

Presymptomatic

Prodromal

Clinical Disease

Neurologic Function

Disease-modifying therapy

Disease Progression
Progression of neurodegenerative diseases

Presymptomatic

Prodromal

Clinical Disease

Disease-modifying therapy

Neurologic Function

Disease Progression
Progression of neurodegenerative diseases

Disease Progression of neurodegenerative diseases

- Presymptomatic
- Prodromal
- Clinical Disease

Disease-modifying therapy

Neurologic Function

Disease Progression
Progression of neurodegenerative diseases

- Presymptomatic
- Prodromal
- Clinical Disease

Disease-modifying therapy
Thanks!

bradd@nmr.mgh.harvard.edu

http://www.dickersonlab.org
http://www.ftd-boston.org

Support
National Institute on Aging, National Institute of Neurological Disorders and Stroke, National Institute of Mental Health, Alzheimer’s Association,