Imaging of Alzheimer’s Disease: State of the Art

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Outline

- Our patient
- Definition of dementia
- Alzheimer’s disease
  - Epidemiology
  - Diagnosis
  - Stages of progression
- Imaging for Alzheimer’s
  - Structural
  - Metabolic
  - Molecular
Our patient: history

**History of present illness:**
- 55-yo man presents with ~2 years of cognitive decline
- Left a high-paying job 5 years ago; no steady job since
- Repeats himself in conversation
- Cannot remember simple tasks
- Low energy, guilt, sadness
- Snores and thrashes at night

**Past medical history:**
- Obstructive sleep apnea
- von Willebrand’s disease

**Medications**
- B12, fish oil

**Family history**
- Father: CAD
- Aunt: dementia

**Social history**
- Highly educated
- No EtOH, drugs
Our patient: exam findings

- General exam: no findings
- Neurologic exam:
  - Constricted affect
  - 25/30 on the MOCA, with 0/5 for delayed recall
  - Slightly increased tone in both arms
  - Otherwise no deficits

<http://www.mocatest.org>
Our patient: differential diagnosis

**Differential diagnosis:**
- Depression
- OSA
- Early-onset dementia

**Tests:**
- B12: normal
- TSH: normal

**Treatment:**
- Citalopram
- CPAP

6 months later:
- Mood and sleep have improved
- Memory has not

Next test: MRI

Axial T2 MRI: BIDMC PACS
Normal scan
You have seen the clinical presentation of a patient with possible Alzheimer’s Disease. Before returning to the diagnosis, let’s continue with a discussion of dementia.
Dementia: definition

**DSM-V:**
- Decline in ≥1 cognitive domain:
  - Learning and memory
  - Language
  - Executive function
  - Attention
  - Perceptual-motor
  - Social cognition
- Interferes with daily living
- Not due to another mental disorder

**Causes:**
- Neurodegenerative
- Vascular
- Neoplastic
- Inflammatory
- Traumatic
- Metabolic
- Infectious
- Epileptic
- Drug-related
Alzheimer’s Disease

- 60-80% of all dementia, with 5.2 million patients in the US
- 6th-leading cause of death
- Alone in top 10 without means of prevention or cure
- Annual cost: $203B directly + $216B for unpaid caregivers
Alzheimer’s diagnosis

- Definitive diagnosis is only made at autopsy, with classic findings of amyloid plaques and tau tangles

* Aβ plaques
* Tau tangles
* Both pathologies on silver stain

*Serrano-Pozo et al., 2011*
What is the role for imaging?

1. Diagnose
2. Predict and track progression
3. Assess treatment response

Imaging biomarkers can precede cognitive symptoms by many years

Jack & Holtzman, 2013
Imaging recommendations

The American College of Radiology recommends imaging in patients with possible or probable Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL*</th>
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</thead>
<tbody>
<tr>
<td>MRI head without contrast</td>
<td>8</td>
<td>This procedure is used in structural evaluation; volumetric determinations are generally not appropriate in routine clinical imaging.</td>
<td>O</td>
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<tr>
<td>MRI head without and with contrast</td>
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<td>See statement regarding contrast in text under “Anticipated Exceptions.”</td>
<td>O</td>
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<tr>
<td>CT head without contrast</td>
<td>6</td>
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<td>**</td>
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<tr>
<td>FDG-PET/CT head</td>
<td>6</td>
<td>This procedure may be used as a problem-solving technique in differentiating dementias.</td>
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<td>CT head without and with contrast</td>
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<tr>
<td>CT head with contrast</td>
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<tr>
<td>MR spectroscopy head without contrast</td>
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<td>MRI functional (fMRI) head without contrast</td>
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<td>This procedure is used for research purposes.</td>
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<td>Tc-99m HMPAO SPECT head</td>
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<tr>
<td>Amyloid PET/CT head</td>
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Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

Wippold et al., 2015
Imaging Modalities

- **Structural: brain volume**
  - MRI
- **Metabolic: brain function**
  - FDG-PET
- **Molecular: protein accumulation**
  - Amyloid
  - Tau
MRI is indicated for two reasons:

1) It excludes other causes of cognitive decline, such as stroke, tumor, and demyelinating disease. Our patient had a normal scan, ruling out these possibilities.

2) It can strengthen the diagnosis of Alzheimer’s Disease by showing a typical pattern of degeneration in the medial temporal lobes. See the next slide for an example.
Structural imaging: MRI

**Alzheimer’s:**
Medial temporal atrophy

**Frontotemporal dementia:**
Frontal atrophy

These patterns of atrophy can precede symptoms by ~10 years, and predict progression from MCI to dementia
Metabolic imaging: FDG-PET

FDG-PET tracks glucose metabolism, a proxy for synaptic activity. Medicare will cover this test to distinguish AD vs. FTD.

Decreased temporal, parietal, and posterior cingulate uptake in AD

Jack & Holtzman, 2013
Metabolic imaging: less common techniques

- **SPECT**: radionuclide technique that measures cerebral blood flow
  - Expect temporo-parietal hypoperfusion in AD
- **fMRI**: measures blood flow as patients perform cognitive tasks
- **MR spectroscopy**: measures metabolite concentrations
  - Expect ↓ N-acetylaspartate and ↑ myoinositol, reflecting neuronal injury
Molecular imaging: amyloid

PET imaging can track amyloid deposition, even before clinical symptoms

Increased amyloid everywhere but primary sensory & motor cortex, and medial temporal lobe

*Jack & Holtzman, 2013*
Molecular imaging: amyloid

- Amyloid PET has high negative predictive value but low positive predictive value.
- 30% of healthy older adults will have elevated amyloid.

*Sperling et al., 2014*
Molecular imaging: amyloid

- Amyloid PET is used as a biomarker in drug trials involving anti-amyloid antibodies.
- The antibodies successfully clear amyloid but do not affect clinical outcome.

*Salloway et al., 2014*
Molecular imaging: tau

PET tracers for tau aggregates are under investigation

Normal

Mild AD: ↑ uptake in temporal lobes

Companion Patients #4 and #5: James et al., 2015
Back to our patient: diagnosis

2 years later:

- Memory deficits persist, but fluctuate between visits
- Spatial skills and orientation remain intact
- Not a classic AD presentation: can imaging clarify?

FDG PET shows AD-specific hypometabolism
On the basis of the FDG-PET results, along with CSF and genetic testing, our patient was diagnosed with AD. He began treatment with donepezil and memantine. Although his prognosis is poor, having the diagnosis helped him and his family prepare for the future. Imaging was a crucial part of this process.
Summary

• We have followed a patient from his initial presentation to the diagnosis of Alzheimer’s Disease.

• We have discussed the definition of dementia, as well as the epidemiology, diagnosis, and stages of progression of Alzheimer’s Disease.

• We have reviewed the indications for imaging in Alzheimer’s Disease, and seen the classic appearance of AD on structural, metabolic, and molecular imaging, reviewing both standard approaches and the state of the art.


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