Dementia Imaging with Amyloid Agents

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Dementia Imaging with Amyloid Agents

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October 21st
Alzheimer’s Disease

1907 publication: “A Unique Illness Involving the Cerebral Cortex”

- 51 y.o. female pt with progressive presenile dementia

2 pathological hallmarks described

- “In the centre of an otherwise almost normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability”

- “Numerous small miliary foci are found in the superior layers. They are determined by the storage of a peculiar material in the cortex”

Alois Alzheimer (1864–1915)
Alzheimer’s Disease

Plaque

Tangle
Alzheimer’s Disease

1950’s – 1970’s

- Recognition that dementia was relatively common
- Growing understanding that “senile dementia” was not a consequence of aging or due to cerebral atherosclerosis
- Senile dementia of the Alzheimer type (> age 65) and Alzheimer's (presenile) dementia were pathologically the same disease
- Disease became known as Alzheimer’s Disease
Alzheimer’s Disease

- McKhann et al. (1984): criteria for the diagnosis of AD (NINDS/ADRDA)
- “Probable AD”
  - Dementia established by clinical examination, confirmed by neuropsychological tests
  - Deficits in 2 or more areas of cognition
  - Progressive worsening
  - Exclusion of other disorders
- “Definite AD”
  - Clinical criteria plus histopathology
  - Amyloid plaques and neurofibrillary tangles
  - Not possible to have a definitive diagnosis antemortem
Frontotemporal Dementias

- 2nd / 3rd most common form of dementia
- Several syndromes involving frontal and temporal lobe dysfunction
  - Behavioral variant (~50% of FTD):
  - Primary progressive aphasia
- Pathology
  - Focal frontal, anterior temporal atrophy
  - “Pick bodies” – tau +ve, argyrophillic inclusions in neurons
- No amyloid
Dementia with Lewy Bodies

- 2nd/3rd most common form of dementia
- Central feature - progressive cognitive decline
- Core features (2/3 for probable DLB)
  - fluctuating cognition, attention, alertness
  - visual hallucinations
  - motor features of parkinsonism

Degeneration of DA neurons
Lewy bodies in neurons (alpha-synuclein, as in PD)
Amyloid pathology often present
Mild Cognitive Impairment

- Characterization of **Mild Cognitive Impairment** (Petersen 1999)
- Clinical criteria
  - Concern reflecting a change in cognition reported by patient or informant
  - Objective evidence of impairment in one or more cognitive domains, typically including memory
  - Preservation of the abilities of daily living
  - Patient not demented
- Often the symptomatic pre-dementia phase of AD
- ~12% of MCI patients convert to AD per year
- Recognition that many MCI patients had AD pathology at autopsy
Alzheimer’s Disease – Clinical Diagnosis

Accuracy of clinical diagnosis of probable AD, using NINCDS/ADRDA 1984 criteria vs. neuropathology

- Knopman, Neurology 2001, literature review
  » sensitivity ~81 %, specificity ~70%

- Beach J Neuropath Exp Neurol 2012
  » U.S. Alzheimer’s Disease Centers, 2005 – 2010
  » sensitivity 71%, specificity 71% (n = 618)
  » for patients with the clinical diagnosis of non-AD dementia (DLB, FTD, etc.)
  39% had AD on pathology (n = 271)
Alzheimer’s Disease ~2000

- Alzheimer’s Disease
  » Accounts for ~ 60% of dementia cases
  » Other causes: DLB, FTDs, vascular, mixed
  » Clinical criteria for dx of probable AD are only ~ 70-80% sensitive, 70% specific, compared to pathological diagnosis

- Mild Cognitive Impairment (MCI)
  » ~ 50% progress to AD in 3-4 years
  » Many MCI patients have pathological changes of AD

- Consensus that excess amyloid is the likely cause of the AD pathophysiological process (amyloid hypothesis)
• > 10,000 PiB PET scans in ~60 research centers performed
  » Sensitive to the clinical dx of AD, Aβ histopathology
  » Frequently positive in MCI, marker for progression to dementia
  » Aβ positivity found in healthy controls, increases with age
[C-11]PIB in Aging and Dementia

Rowe et al., Neurology 2007
Model for the Time Course of AD Pathophysiology

Jack, Radiology (2012), 263(2): 244
F-18 Amyloid Radiotracers

- **AZD2184** (AZ/Navidea)
- **AZD4694** (AZ/Navidea)
- **PiB** (GE Healthcare)
- **3'-F-PiB GE-067 Flutemetamol** (GE Healthcare)
- **SB-13** (Bayer/Piramal)
- **AV-1 BAY94-9172 Florbetaben** (Bayer/Piramal)
- **AV-45 Florbetapir Amyvid™** (Avid/Lilly)

Mathis Sem NM 2012
F-18 Amyloid Radiotracers

Rowe and Villemagne 2011
F-18 Florbetapir Validation

N=29
N=14 Amyloid –ve autopsy
14/14 PET –ve
100% specific for amyloid

N=15 Amyloid +ve autopsy
14/15 PET +ve
93% sensitivity

Clark et al., JAMA 2011
April 2012 U.S. FDA approval of [F-18]florbetapir

• “… for PET imaging of the brain to estimate Aβ in patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.”

• “A -ve scan indicates sparse to no Aβ and is inconsistent with a neuropathological diagnosis of AD; it reduces the likelihood that a patient’s cognitive impairment is due to AD.”

• “A +ve scan indicates moderate to frequent Aβ plaques; this amount of Aβ is present in patients with AD, but may also be present in patients with other neurologic conditions as well as in older people with normal cognition.”
AA-SNMMI Task Force on Appropriate Use Criteria (AUC) for Amyloid PET Imaging

- Formed in March, 2012
- Goal – to develop AUC to guide the clinical use of Aβ imaging
- Approach
  » Consider possible clinical scenarios for use of Aβ imaging
  » Evaluate published research and assess evidence supporting use of imaging in these scenarios
  » Classify scenarios as appropriate or not appropriate, based on the available evidence and expert consensus opinion
  » Produce a consensus report, discussing scenarios and other issues related to Aβ imaging - March 2013 in JNM
AUC for Amyloid Imaging

**Preamble**
Amyloid imaging is appropriate for the 3 listed indications for individuals with all of the following characteristics:

1. a cognitive complaint with objectively confirmed impairment
2. AD as a possible dx, but when the dx is uncertain after a comprehensive evaluation by a dementia expert
3. when knowledge of the presence or absence of Aβ pathology is expected to increase diagnostic certainty and alter management

**Indications**
1. Patients with persistent or progressive unexplained MCI
2. Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation
3. Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age)

**Non-Indications**
4. Patients with core clinical criteria for probable AD with typical age of onset
5. To determine dementia severity
6. Based solely on a positive family history of dementia or presence of (APOE )ε4
7. Patients with a cognitive complaint that is unconfirmed on clinical examination
8. In lieu of genotyping for suspected autosomal mutation carriers
9. In asymptomatic individuals
10. Nonmedical use (e.g., legal, insurance coverage, or employment screening)
Preamble

Amyloid imaging is appropriate for the 3 listed indications for individuals with:

i. a cognitive complaint with objectively confirmed impairment

ii. AD is a possible dx, but the dx is uncertain after a comprehensive evaluation by a dementia expert

iii. knowledge of the presence or absence of Aβ pathology is expected to increase diagnostic certainty and alter management
1. Patients with persistent or progressive unexplained MCI

- A +ve scan raises the level of certainty that the patient’s impairment is based on AD pathology and represents early AD
- Prognosis. Reports suggest that the majority of patients with amnestic MCI and a +ve scan will progress to AD dementia; the risk of progression is significantly lower in those who are amyloid -ve
2. Patients satisfying core clinical criteria for possible AD, but with unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation

- There is substantial doubt about whether the dementia is based on AD pathology
  
  (i) an unusual course (e.g., sudden onset or episodic) or because the course cannot be established from the history
  
  (ii) a comorbid condition that confounds the interpretation of the clinical data, e.g., cerebrovascular disease
Appropriate Indications

3. Patients with progressive dementia and atypically early age of onset (usually defined < 65 y.o.)

- Pts often harder to diagnose, may have features of AD as well as of a non-AD dementia, FTD more common
- Purpose is to manage symptomatic treatment; make appropriate employment and lifestyle decisions; possibly refer the patient to a clinical trial; and provide a basis for prognosis and planning for care
Non – Indications for Aβ Imaging

4. Patients with core clinical criteria for probable AD with typical age of onset

• Level of uncertainty is low
• The potential benefit from added information and for altered management is correspondingly low
Non – Indications for $\text{A}\beta$ Imaging

5. To determine dementia severity
   - $\text{A}\beta$ burden measured with PET does not correlate well with dementia severity
   - This is a clinical assessment

6. Based solely on a positive family history of dementia or presence of $\text{APOE } \varepsilon 4$
   - No data that indicate that $\text{A}\beta$ imaging helps the assessment of prognosis or course
Non – Indications for Aβ Imaging

7. Patients with a cognitive complaint that is unconfirmed on clinical examination
   • No evidence to suggest PET aids in prognosis

8. In lieu of genotyping for suspected autosomal mutation carriers
   • The optimal evaluation in these cases is careful family history, followed (if appropriate) by counseling before and after genetic testing
Non – Indications for Aβ Imaging

9. In asymptomatic individuals
   - The prognostic value of Aβ positivity in normal elderly individuals is investigational
   - There is a potential for patients and families to make inaccurate assumptions about risk and future outcomes on the basis of PET results

10. Nonmedical use (e.g., legal issues, insurance coverage, or employment screening)
   - No evidence to support use outside of a diagnostic evaluation
     » competency, insurability, work activities
     » ability to drive or make financial decisions
Preamble:
(iii) Dementia expert must determine that an Aβ PET scan would increase the level of diagnostic certainty and alter the plan for patient management

1. Medication management
2. Change in ordering other tests
3. Value of knowing
1. Medication Management

• A +ve scan that raises confidence in the dx of AD is likely to result in earlier and appropriate use of specific medications, e.g., ACh inhibitors, memantine

• It may be inappropriate to start or continue these medications in patients with a -ve scan

• Realize current Rx is symptomatic, modest effects
## Medication Management

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<tr>
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<th>Anti-AChE</th>
<th>Anti-psychotics</th>
<th>Anti-amyloid</th>
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<tbody>
<tr>
<td>AD</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DLB</td>
<td>+</td>
<td>- -</td>
<td>-</td>
</tr>
<tr>
<td>FTD</td>
<td>-</td>
<td>+</td>
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</table>
2. Change in Ordering Other Tests

- A PET scan may reduce the use of other tests and repeated tests (imaging, neuropsychology) that are costly and burdensome to patients and caregivers.

- Data are needed to see if this happens.
3. Value of Knowing

- Survey data indicate that most individuals would want to know that if they or a family member were exhibiting confusion and memory loss, the cause was AD.

- A more certain diagnosis can have major social benefits to patients and families, who need to plan for the future:
  - Counseling, advance directives, finances, career choices, driving, future care planning.

Image Quality and Reporting

- Scans should be performed under the supervision of and interpreted by a physician certified in NM or nuclear radiology.
- The physician must be familiar with brain anatomy and must have training in amyloid PET interpretation.
  - Package insert for [F-18]florbetapir: “Images should be interpreted only by readers who successfully complete a special training program.”
  - Training offered by SNMMI, by manufacturer.
- Interpretation is performed independently of the patient’s clinical features.
- Scans should be reported as +ve or –ve for the presence of Aβ; not for a diagnosis of dementia or AD.
Image Quality and Reporting

- Images displayed in B/W, appropriately scaled
- Consider technical difficulties: blurring due to pt. motion, noisy image due to incomplete radiotracer injections, cortical atrophy

Amyvid (Florbetapir F 18 Injection) package insert
Areas for Future Work

For molecular imaging community

- Quality of image interpretation and reporting, effect of training programs for readers
- Define relative roles of Aβ tracers, FDG, I-123 ioflupane
- Use of quantitative methods to assess radiotracer uptake; SUVr, automated reading programs
- Development of procedure guidelines to standardize imaging (SNMMI, EANM)
- Comparison of the performance of different F-18 labeled Aβ radiotracers in the same patients
- Development of radiotracers for tau (AD, FTD, CTE)
Roles of different tracers: C-11 PIB vs. FDG

Rabinovici, Neurology 2011
AD (n=62) vs. FTD (n=45)

PIB scans – visual reads
- Sensitivity for AD – 90%
- Specificity – 83%
- High inter-rater $\kappa = 0.96$

FDG scans – visual reads
- Sensitivity – 78%
- Specificity – 84%
- Inter-rater $\kappa = 0.72$
Roles of different tracers: I-123 Ioflupane in DLB

- I-123 ioflupane SPECT is approved for evaluation of parkinsonian syndromes
- DA degeneration in DLB, evident on SPECT, PET
- Walker JNNP, 2007
  - Clinical dementia diagnosis (AD, DLB) versus autopsy
  - Sensitivity 88%, specificity 100% for DLB

Images of brain scans:
- Normal
- DLB
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<tr>
<th></th>
<th>AD</th>
<th>DLB</th>
<th>FTD</th>
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<tbody>
<tr>
<td>PET Aβ</td>
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<td>+/-</td>
<td>-</td>
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<tr>
<td>SPECT DAT</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>PET FDG</td>
<td>Temp, Par</td>
<td>Temp, Par + O</td>
<td>Anterior F, T</td>
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Areas for Future Work

For dementia and MI community

- Definition of dementia expert / referring physician (AIT)
- Use in pt. populations outside of the clinical research/academic environment
- Prognosis of a +ve scan in MCI, healthy subjects
- Relationship to other biomarkers – CSF, MRI
- Impact on patient management (medication use, use of other tests) and ultimate patient health outcomes
- Role in anti-AD drug trials, eventual drug prescribing
Amyloid Imaging in Clinical Trials in AD

- Clinical trials of new drugs often incorporate Aβ imaging
- Subject selection for AD Rx trial
  » Confirm the dx
  » Identify subjects with amyloid and AD in the preclinical phase
- For trials of anti-amyloid Rx
  » Confirm presence of the molecular target
  » As a biomarker, to monitor effect of therapy
Amyloid Imaging in Clinical Trials in AD

$^{11}$C-PiB PET assessment of change in fibrillar amyloid-$\beta$ load in patients with Alzheimer’s disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

*Lancet Neurol* 2010; 9: 363-72


![Graph showing estimated mean change from baseline in $^{11}$C-PiB over weeks with placebo and bapineuzumab](image-url)
Thank You!