Update on Molecular Imaging in Dementia

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Disclosure Information
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• I have the following financial relationships to disclose:

  Consultant for:
  Eli Lilly/Avid
  GE Healthcare
  Blue Earth Diagnostics
  Alpha Source (spouse)

  Grant/Research support from:
  Eli Lilly/Avid
  ABBVie (spouse)

• I will discuss the following off label use and/or investigational use in my presentation:
  Investigational Tau-PET tracers
  Off-label use of [123I]Ioflupane

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75 Years of Dedication to Our Members

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Outline of presentation

• Overview
• FDG-PET
• Amyloid-PET
• Future directions
• Cases
About a peculiar disease of the cerebral cortex...

“There are without any doubt many more psychic illnesses than listed in our textbooks. In some of these instances a later histological examination will subsequently reveal peculiarities of the specific case. Then, we will gradually arrive at a stage, when we will be able to separate out individual disease from the large illness categories of our textbooks; to delineate them clinically more accurately.”

- from the first case report of Alzheimer’s dementia in 1907 by Dr. Alois Alzheimer
Neuritic plaques containing amyloid and neurofibrillary tangles containing tau are key features of Alzheimer’s disease.

Proteinopathies in neurodegenerative diseases

Core clinical criteria for dementia

- Based on cognitive or behavioral symptoms that:
  - Interfere with ability to function
  - Represent a decline from previous level of function
  - Not explained by delirium or psychiatric disorder

- Typically insidious onset

- Impairment is detected and diagnosed through history-taking from the patient and an informant and objective cognitive assessment

Mild cognitive impairment (MCI)

• Same clinical criteria as dementia except there is **no interference with usual activities**
  – often comes to clinical attention through self-reporting
  – can be detected on neuropsychological testing

• **Prognosis of MCI is variable** and depends on the etiology
  – may be the beginning of dementia
  – may be stable for years
  – may resolve (e.g. depression, medication related)
Key clinical features of dementia due to AD

• Initial and most prominent cognitive deficits are typically in one of the two following categories:
  
  – **amnestic presentation** including learning and recall of recently learned information (most common)
  
  – **non-amnestic presentations**
    • language (esp. word finding)
    • visuospatial
    • executive dysfunction

Accuracy of clinical diagnosis of AD dementia

• Clinical diagnosis of probable AD dementia is approximately 80% concordant with pathology
  – may be better at dementia centers (~90%)
  – may be challenging in first patient encounters

• Diagnostic accuracy for other causes of dementia may be substantially lower
  – Dementia with Lewy bodies (DLB)
  – Frontotemporal dementia (FTD)

• Neurodegeneration is advanced at the time of clinical diagnosis
  – may not be adequate for selecting patients for clinical trials
  – important implications for therapy
Diagnostic considerations in patients with cognitive impairment

- Relatively common types of dementia:
  1) Alzheimer’s dementia (AD)
  2) Dementia with Lewy bodies (DLB)
  3) Frontotemporal dementia (FTD)
  4) Vascular dementia (VaD)
  5) Parkinson’s disease (PD)

- Rare types of dementia

- Mild cognitive impairment (MCI)

- Non-degenerative etiologies
Goals of biomarkers in dementia

• Increase specificity and certainty in the diagnosis of dementing diseases

• Understand the time course of the pathophysiology of dementing diseases

• Select appropriate individuals at high risk for dementia for clinical trials and therapy

• Monitor response to therapies

• Identify prospectively individuals that would benefit from therapy prior to irreversible cognitive decline
Nuclear Toolbox for Dementia Imaging

**Brain Perfusion**
- ECD
- HMPAO

**Glucose Metabolism**
- FDG

**Dopamine transporters**
- Ioflupane

**Beta-amyloid**
- Flutemetamol
- PiB
- Florbetaben
- Florbetapir

**Tau**
- T807
- THK-5105 (R=CH₃) and 5117 (R=H)
- PBB3
- THK-5351
Time course of biomarkers in Alzheimer’s Disease

Adapted from Alzheimer’s Disease Neuroimaging Initiative (ADNI) http://adni.loni.ucla.edu/about/biomarkers/brain MR/.
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FDG for neuroimaging

• 2-deoxy-2-$[^{18}\text{F}]$fluoro-D-glucose (FDG) is a glucose analogue that is widely used clinically

• Cellular uptake and retention of FDG is a marker of glycolysis

• The brain uses glucose as its primary source of energy and has high physiologic levels of FDG uptake
  – FDG uptake is a marker of synaptic activity and neuronal density

• For clinical neuroimaging, FDG is used primarily for dementia, neuro-oncology, and epilepsy
Normal brain $[^{18}\text{F}]$FDG-PET
Normal brain $[^{18}\text{F}]$FDG-PET
FDG-PET for dementia

• Changes in FDG uptake in the brain can be altered by many physiologic and pathologic factors
  – clinical context is critical
  – correlative structural imaging may be useful

• Decreases in FDG uptake in dementia occur due to loss of synaptic activity and neuronal loss
  – FDG is a marker of neuronal injury and dysfunction

• Pattern of FDG uptake provides specificity of diagnosis
[\textsuperscript{18}F]FDG-PET for Alzheimer’s disease

- Sensitivity for detection of AD is about 90% with specificity of 71-73% based on autopsy data
  - lower specificity is due to overlap with other dementias
  - for AD versus FTD, the specificity is higher (~85-95%)

- Typical uses of [\textsuperscript{18}F]FDG-PET in dementia
  - distinguish AD from FTD
  - evaluate early-onset (ages 45-64) or atypical dementia

Typical patterns of FDG hypometabolism in AD, DLB, and FTD

**AD pattern:** posterior parietotemporal

**DLB pattern:** AD pattern plus occipital

**FTD pattern:** anterior frontal and/or temporal
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Amyloid plaque imaging agents: Pittsburgh Compound B (PiB)

[11C]PiB has been used extensively in research studies for amyloid plaque imaging.

Thioflavin S staining of amyloid plaques and neurofibrillary tangles in a patient with AD

Image Courtesy of Dr. Nigel Cairns and the ADRC Neuropathology Core at Washington University in St. Louis
PET tracers for amyloid plaque imaging

\[ ^{[11}C]\text{PiB} \]

\[ ^{[18}F]\text{florbetapir (Ely Lilly/Avid)} \]

\[ ^{[18}F]\text{flutemetamol (GE)} \]

\[ ^{[18}F]\text{florbetaben (Piramal, formerly Bayer-Schering)} \]

\[ ^{[18}F]\text{AZD4694 (Navidea, formerly Astra-Zeneca)} \]

Diagnostic performance of $^{18}$F-labeled amyloid PET tracers in clinical trials

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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</thead>
<tbody>
<tr>
<td>Florbetaben</td>
<td>98 (96-98)</td>
<td>80 (77-83)</td>
</tr>
<tr>
<td>Florbetapir</td>
<td>92 (69-95)</td>
<td>95 (90-100)</td>
</tr>
<tr>
<td>Flutemetamol</td>
<td>88 (81-93)</td>
<td>88 (44-92)</td>
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</tbody>
</table>

Sensitivity and specificity shown as median from multiple readers in bold and range of readers in parentheses. Data from interpretations after in-person training.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202008s000lbl.pdf (florbetapir)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203137s000lbl.pdf (flutemetamol)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf (florbetaben)
Implications of amyloid-PET results

• Amyloid-PET serves as a biomarker for pathological amyloid deposition

• Amyloid pathology is thought to precede clinical findings of dementia by 10-25 years
  – AD pathophysiology ≠ AD dementia

• A negative amyloid-PET scan makes Alzheimer’s disease unlikely as the cause of a patient’s cognitive impairment

• A positive amyloid PET does not establish the diagnosis of AD or other neurological disorders
Comparison of negative (top) and positive (bottom) amyloid-PET scans.
β-amyloid plaque deposition precedes AD dementia

Adapted from Rowe CC et al., 2010. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, Neurobiol Aging. 31:1275-83.
Imaging of disease time course in autosomal dominant AD

PIB (amyloid)

FDG (metabolism)

Thickness (neurodegeneration)

<table>
<thead>
<tr>
<th>EYO</th>
<th>-15</th>
<th>-10</th>
<th>-5</th>
<th>0</th>
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</thead>
<tbody>
<tr>
<td>A)</td>
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<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<td>B)</td>
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<td>C)</td>
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</table>

EYO Estimated years to onset of symptoms
EYO = parents age of onset – current participant age

Appropriate use criteria (AUC) for amyloid-PET

• Patients considered for amyloid PET should have the following characteristics:
  – Cognitive complaint with objectively confirmed impairment
  – AD as a possible diagnosis with uncertainty remaining after comprehensive evaluation by a dementia expert
  – Knowledge of amyloid status will increase diagnostic certainty and alter management

Coverage with Evidence Development (CED)

- Amyloid Imaging Coverage with Evidence Development workgroup submitted a protocol to CMS for PET amyloid imaging in patients satisfying the AUC

- “IDEAS” Study: Imaging Dementia - Evidence for Amyloid Scanning
  - Began enrolling in February 2016
  - makes amyloid-PET reimbursable clinically when performed as part of CED
IDEAS Study

• Open-label, longitudinal cohort study to assess the impact of amyloid PET on patient outcomes in patients meeting AUC

• The primary hypothesis is that, in diagnostically uncertain cases, knowledge of amyloid status as determined by amyloid PET will change patient management and improve medical outcomes

• Patients will be recruited into one of two sub-cohorts:
  – Progressive, unexplained mild cognitive impairment (MCI)
  – Dementia of uncertain etiology
• Test whether amyloid PET imaging will lead to a $\geq 30\%$ change between intended and actual patient management within $\sim 90$ days in a composite measure of at least one of the following:

  - AD drug therapy
  - Other drug therapy
  - Counseling about safety and future planning

• The hypothesis will be tested separately for MCI and dementia
IDEAS Aim 2

• To assess the impact of brain amyloid PET on hospital admissions and emergency room visits in study patients (amyloid PET-known) compared to matched patients not in the study (amyloid PET-naïve) over a 12 month interval

- CMS Claims Data to address Aim 2 will be collected for all study participants and from concurrent controls matched according to a validated algorithm
Qualified Dementia Specialists and PET Facilities register at ideas-study.org (Registration opened on Sept. 30, 2015)

Dementia Specialist:
Screen and Consent Participants (T1)
Enrollment started in Feb. 2016

Refer for Amyloid PET Scan

Amyloid PET Scan within 30 Days after T1 (T2)

Treating Physician: Visit with Pt to Complete 90-Day Post-Amyloid PET Assessment (T3)

Submit Pre-PET CRFs within 30 Days before Amyloid PET Scan (Aims 1 & 2)

Submit PET Report and PET CRF and PET images within 7 Days after Amyloid PET (Aims 1 & 2)

Submit Post-PET CRF within 15 Days after T3 Visit (Aim 1)
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Emerging tracers for neuroimaging in patients with cognitive impairment

• **Ioflupane** for dopaminergic imaging
  - relevant to dementia with Lewy bodies (DLB) and certain other less common neurodegenerative diseases

• **Tau imaging** with novel PET tracers
  - relevant to Alzheimer’s disease, certain forms of FTD and other neurodegenerative diseases with tauopathies
[\textsuperscript{123}I]Ioflupane for dopamine transporter (DAT) imaging

- FDA approval is for distinguishing Parkinsonian syndromes (PS) from essential tremor
  - striatal DAT is lost in Parkinson’s disease and PS but not essential tremor and drug induced parkinsonianism
  - high positive and negative agreement (>90%) with clinical diagnosis in patients with and without Parkinsonian syndromes

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022454s000ltr.pdf (ioflupane)
Loss of dopaminergic neurons is a hallmark of Parkinson’s disease and syndromes

Brain Ioflupane-SPECT

55 year old woman with hand tremor

Normal Ioflupane study

62 year old woman with stiffness, difficulty walking and hallucinations

Abnormal Ioflupane study
Loss of dopaminergic neurons precedes symptomatic Parkinson’s disease

Loss of dopaminergic neurons is shown to occur before the onset of motor symptoms. This is illustrated in the graph, where the percentage of dopaminergic neurons remaining is plotted against patient age. Different lines represent normal aging, idiopathic PD, environmental exposure, and early onset PD. The graph shows that even before the onset of motor symptoms, there is a significant loss of dopaminergic neurons.

Parkinsonian syndromes associated with DAT loss

- Parkinson’s disease (PD)
- Dementia with Lewy bodies (DLB)
- Corticobasal degeneration (CBD)
- Multiple system atrophy (MSA)
- Progressive supranuclear palsy (PSP)

- Ioflupane-SPECT can distinguish DLB from AD and FTD but it not part of the FDA-approved use of ioflupane
  - mean sensitivity for probable DLB = 78%
  - mean specificity for probable DLB = 90%
  - clinical diagnosis used as reference standard

Tau imaging

• Several PET tracers are being used in human studies to measure brain tau
  – currently only used on a research basis

• Pathological tau deposition appears to occur in temporal association with cognitive impairment and neurodegeneration

• Tau is not specific to a particular neurodegenerative disease
Spread of tau pathology in AD

Stage 1-2: Transentorhinal
Stage 3-4: Limbic
Stage 5-6: Isocortical


Slide courtesy of Tammie Benzinger M.D., Ph.D.
Putative role of tau in the pathophysiology of AD

### Therapeutics targeting tau in development

<table>
<thead>
<tr>
<th>Drug name, category and clinical trials</th>
<th>Mechanism of action</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tau aggregation or deposition inhibitors</strong></td>
<td></td>
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<tr>
<td>Fachixaal</td>
<td>Tau deposition and aggregation inhibitor; microtubule stabilizing agent.</td>
<td>Generic</td>
</tr>
<tr>
<td>Davuneptide, AL-106, NAP Phase II clinical trial in mC1 patients: negative</td>
<td>Tau deposition and aggregation inhibitor; microtubule stabilizing agent.</td>
<td>Alion Therapeutics-Biogen Idec</td>
</tr>
<tr>
<td>BMS-241027</td>
<td>Tau deposition and aggregation inhibitor; microtubule stabilizing agent.</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>TbO237. (methylthioninium chloride, methylene blue) LMTX: two Phase III clinical trials</td>
<td>Inhibitor of tau protein aggregation</td>
<td>University of Aberdeen, UK, and TauRx Therapeutics</td>
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<tr>
<td>Pyridazines</td>
<td>Tau aggregation inhibitors</td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td>BLY-0703</td>
<td>Tau aggregation inhibitor</td>
<td>BioAlvo</td>
</tr>
<tr>
<td>ReMIND NV</td>
<td>Tau deposition inhibitor</td>
<td>Roche</td>
</tr>
<tr>
<td>Nicotinamide Phase II clinical trial</td>
<td>Inhibitor of microtubule polymerization</td>
<td>Generic</td>
</tr>
<tr>
<td><strong>Kinase inhibitors</strong></td>
<td></td>
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<tr>
<td>GSK-3 inhibitors (various)</td>
<td>Kinase inhibition (GSK-3)</td>
<td>AstraZeneca, Takeda, CrystalGenomics</td>
</tr>
<tr>
<td>Valproate, divalproex sodium Phase III clinical trial: negative and worsening</td>
<td>Inhibitor of the kinase GSK-3</td>
<td>Generic</td>
</tr>
<tr>
<td>Tidogrub, NPO3112, NP-12 Two Phase II clinical trials</td>
<td>Inhibitor of the kinase GSK-3</td>
<td>Noscira</td>
</tr>
<tr>
<td>SAN-161</td>
<td>Inhibitor of the kinase GSK-3</td>
<td>Sancimmune</td>
</tr>
<tr>
<td>Lithium chloride: two negative and one positive Phase II clinical trials</td>
<td>Kinase inhibitor</td>
<td>Generc</td>
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<tr>
<td>Tau protein modulators</td>
<td>Enzyme modulator</td>
<td>Biogen Idec</td>
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<tr>
<td><strong>Immunotherapeutics</strong></td>
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<tr>
<td>Monoclonal antibodies</td>
<td>Passive tau immunization</td>
<td>AC Immune, Prothera Elan, Neotope Biosciences</td>
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<td>Supra-antigen vaccines</td>
<td>Active tau immunization</td>
<td>AC Immune</td>
</tr>
<tr>
<td>AAVDvac-1 clinical Phase VII</td>
<td>Vaccine : synthetic peptide targeting pathological tau protein</td>
<td>Axon Neuroscience</td>
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<tr>
<td>GSK-3: Glycogen synthase kinase 3.</td>
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Progression from normal to asymptomatic to symptomatic AD
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Case

• HISTORY: 47-year-old woman with rapidly progressive dementia and positive paraneoplastic panel (anti-ganglionic acetylcholine receptor). The study is requested for diagnosis of unknown primary malignancy as an etiology of a paraneoplastic syndrome.
Final Diagnosis

• Early onset Alzheimer’s disease
  – clinical course consistent with diagnosis
Case 2

• 78 year old man with memory and thinking problems reported by wife since age 57
Case 2

Amyloid PET

Tau PET
Case 2 summary

- Amyloid and tau PET negative
- MR volumes normal
- Cognitively intact
- Normal studies, stage 0
Case 3

- 87 year old man with subtle memory changes beginning at 77
  - MMSE = 30, on donepezil
Case 3

Amyloid PET

Tau PET
Case 3 summary

- Amyloid positive, tau negative PET studies
- Stable subtle cognitive impairment
- Stage 1 preclinical AD
Case 4

- 73 year old man with no cognitive complaints, MMSE 30
Case 4

Amyloid PET

Tau PET
Case 4 summary

• Amyloid positive and subtle tau positive PET
• Cognitively intact
• Suspect stage 2 presymptomatic AD
Case 5

- 76 year old woman with gradual onset of cognitive impairment, now moderate in severity
Case 5

Amyloid PET

Tau PET
Case 5 summary

- Amyloid and tau PET positive
- Hippocampal atrophy on MRI
- Clinical evaluation shows progressive cognitive impairment
- Symptomatic AD with concordant imaging biomarkers
Potential neuroimaging algorithm for dementia for AD, DLB, and FTD

MRI for structure, volume, functional imaging
-dementia remains in the DDx

FDG-PET for glucose metabolism
-normal FDG-PET
-no dementia

FDG-PET: AD or DLB pattern

FDG-PET: FTD or other pattern

normal ioflupane
-AD

abnormal ioflupane
-DLB

negative amyloid
-FTD

positive amyloid
-AD

Adapted from Kirk Frey, U Michigan
Summary

• A range of molecular imaging agents are clinically available including FDG, amyloid tracers, and ioflupane

• Coverage with evidence development will likely increase the clinical use of molecular neuroimaging

• Tau-PET represent a new class of investigational tracers for Alzheimer’s disease and some other neurodegenerative diseases

• If disease-modifying therapies become available, the volume of molecular neuroimaging will likely increase dramatically
Research support

- The Charles F. and Joanne Knight Alzheimer’s Research Initiative
- Support from Fred Simmons and Olga Mohan
- NIH/NIA P01AG026276, P01AG003991, P50AG05681, 2UL1TR000448
- Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly)

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