ADVANCES IN NEUROIMAGING OF DEMENTIA

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☐ No financial disclosure
Content

- New role of neuroimaging in dementia
- Downstream Imaging Biomarkers
- Upstream Imaging Biomarkers
Cognitive Impairment
AGING? DEMENTIA? DEPRESSION? METABOLIC?
INFECTION? POST-CHEMOTHERAPY? POST-STROKE?
POST-ANESTHESIA? OR OTHERS???
Reliability of Clinical Diagnosis of Dementia

- Clinical versus ‘neuropathology as gold standard’, for example:
  - NINCDS-ADRSA (1984) : Probable AD
  - DSM-III-R : Dementia of the Alzheimer type
  - These criteria proved to be moderately reliable for the diagnosis of probable AD, with a sensitivity of 81% (range: 49-100%) and specificity of 70% (range: 47-100%) or vice versa

Challenges to Structural and Functional Neuroimaging

- surrogate marker/adjunct for diagnosis of AD: early and specific, preclinical stage, phenotypes and other dementias
- monitoring of intervention: sensitivity to therapeutic response, repetitive use
- application in clinical setting: visual vs quantitative, cross-sectional vs longitudinal
Diagnostic criteria for AD

- Probable AD: A plus one or more supportive features B, C, D, or E

A. Core diagnostic criteria

... 

B. Presence of medial temporal lobe atrophy

- Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C. Abnormal cerebrospinal fluid biomarker

... 

D. Specific pattern on functional neuroimaging with PET

- Reduced glucose metabolism in bilateral temporal parietal regions

- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

Time course of Alzheimer’s disease

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>With three levels of evidence of AD pathophysiological process</td>
<td>Intermediate</td>
<td>Unavailable or indeterminate</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>Positive</td>
<td>Unavailable or indeterminate</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>With evidence of AD pathophysiological process</td>
<td>High but does not rule out second etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Dementia-unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, \(^{18}\)fluorodeoxyglucose; MRI, magnetic resonance imaging.
DOWNSTREAM BIOMARKERS
Hippocampal Atrophy
Visual assessment of Medial Temporal Lobe atrophy by MRI

### Table 1: Scheme of medial temporal lobe atrophy rating

<table>
<thead>
<tr>
<th>Score</th>
<th>Width of choroid fissure</th>
<th>Width of temporal horn</th>
<th>Height of hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>3</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>4</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>

A score of 0 to 4 is given separately for the left and right side.  
(↑) = increase; (↓) = decrease.
Figure 3. Post-test probability of disease with a test of sensitivity 85% and specificity 88% for any given pretest probability (prevalence of disease). The upper curve shows the incremental diagnostic gain from a positive result of a test (i.e., presence of hippocampal atrophy on MRI) and the lower curve shows that from a negative result (i.e., presence of hippocampal atrophy on MRI).
Hippocampal volumetry

MR-based hippocampal volumetry in the diagnosis of Alzheimer’s disease

Clifford R. Jack, Jr., MD; Ronald C. Petersen, PhD, MD; Peter C. O’Brien, PhD; and Eric G. Tangles, MD
Hippocampal volumetry
Figure 4. Hippocampal formation volumetry. Scatter plot and linear regression of normalized HF (HF/TIV $\times 10^3$) on age for control and DAT subjects.
Who is AD?
Mixed Dementia

Binswanger’s Disease

Perfusion

Tc99m ECD SPECT (18F-FDG PET)   DSC MR perfusion
                              ASL MR Perfusion
Assessing utility of single photon emission computed tomography (SPECT) scan in Alzheimer disease: Correlation with cognitive severity.
Axial Tc-99m ECD SPECT

Multi-infarct Dementia
Axial Tc-99m ECD SPECT

PSP
Arterial Spin Labeling MR perfusion

- Intrinsic water as contrast, **NON-INVASIVE**
- Absolute quantification of regional cerebral blood flow (rCBF)
- Other than CBF, probe into hemodynamic parameters such as arterial transit time (aTT), arterial blood volume (aBV) etc.
Patterns of cerebral hypoperfusion in AD & MCI measured with ASL MR Imaging

AD vs CN

18F-FDG PET in AD

18F-FDG PET

Who is AD?
PROTON MAGNETIC RESONANCE SPECTROSCOPY ($^1$H-MRS)
<table>
<thead>
<tr>
<th>Function</th>
<th>Change in aMCI / AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N-acetyl-aspartate (NAA)</strong></td>
<td>Neuronal marker, [NAA] correlates with neuronal density and function</td>
</tr>
<tr>
<td><strong>Creatine (Cr)</strong></td>
<td>Cerebral energy metabolism marker, relatively stable</td>
</tr>
<tr>
<td><strong>Choline (Cho)</strong></td>
<td>Phospholipid metabolism, reflect membrane synthesis and degradation</td>
</tr>
<tr>
<td><strong>Myo-inositol (mI)</strong></td>
<td>Astrocyte/Glial cell marker</td>
</tr>
<tr>
<td><strong>Glutamate (Glu) + Glutamine (Gln) (= Glx)</strong></td>
<td>Glu excitatory neurotransmitter, Gln precursor/regulatory</td>
</tr>
<tr>
<td><strong>Gamma aminobutyric acid (GABA)</strong></td>
<td>inhibitory neurotransmitter</td>
</tr>
</tbody>
</table>
UPSTREAM BIOMARKERS
1. Patients with unexplained progressive Mild Cognitive Impairment

2. Patients with progressive early dementia (below 65 years of age)

3. Patients with atypical clinical course of AD or etiologically mixed
AMYLOID & TAU PET IMAGING
2002

\[
\begin{align*}
\text{[N-methyl-}^{11}\text{C}]\text{PIB}
\end{align*}
\]

2013

18-F Flutemetamol
(or 18-F Florbetapir 2012)
(or 18-F Florbetaben 2014)
Amyloid Binding
Association cortex
(frontal > parietal > temporal > occipital),
- Striatum

18F-Florbetapir, Wolk, JAMA, 2012
MCBP- mean cortical binding potential

Mintun et al., Neurology 2006
## Prevalence of Amyloid PET Positivity in Dementia Syndromes

**A Meta-analysis**

<table>
<thead>
<tr>
<th>AD dementia</th>
<th>Total subjects</th>
<th>Amyloid Positivity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APOE ε4 +</strong></td>
<td>593</td>
<td>Age 60y: 96 (93-98)</td>
</tr>
<tr>
<td><strong>APOE ε4 –</strong></td>
<td>377</td>
<td>Age 80y: 93 (89-95)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dementia with Lewy bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APOE ε4 carrier</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>APOE ε4 noncarrier</strong></td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Frontotemporal dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APOE ε4 carrier</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>APOE ε4 noncarrier</strong></td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APOE ε4 carrier</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>APOE ε4 noncarrier</strong></td>
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### CONCLUSIONS AND RELEVANCE

Among participants with dementia, the prevalence of amyloid positivity was associated with clinical diagnosis, age, and APOE genotype. These findings indicate the potential clinical utility of amyloid imaging for differential diagnosis in early-onset dementia and to support the clinical diagnosis of participants with AD dementia and noncarrier APOE ε4 status who are older than 70 years.

Ossenkoppele et al., JAMA, 2015
AMYLOID PET

Normal

Abnormal

TAU PET

CN elderly MMSE-30

Mild AD MMSE-22

James et al., Frontiers in Neurology, 2015
This new tau PET tracer shows low uptake in controls, intermediate uptake in mild cognitive impairment, and intense tau pathology spreading across the frontal and temporal cortex in Alzheimer’s disease. [Image courtesy of Nobuyuki Okamura, Tohoku University.]
Voxelwise comparisons between 16 controls and four patients with posterior cortical atrophy, a visual variant of Alzheimer’s disease, using $^{18}$F AV1451 PET (tau pathology, green), $^{18}$F FDG PET (glucose metabolism, red), and $^{11}$C PIB (amyloid deposition, blue). This figure demonstrates that tau aggregations strikingly mirror the posterior hypometabolic pattern on FDG-PET, while amyloid deposition is present in both clinically affected posterior regions and less-affected frontal areas.

[Image courtesy of Rik Ossenkoppele and Gil Rabinovici.]
Voxelwise comparison of AV1451 retention in five people with progressive supranuclear palsy versus normal controls shows increased signal in globus pallidus, substantia nigra and subthalamic nucleus in this tau disease. [Image courtesy of Gil Rabinovici and Bill Jagust.]
AD - F/64, HK-MoCA:20, FHx+

VD - F/78, HK-MOCA:7

SCD – F/75, HK-MOCA:28
Proposed biomarkers (MRI-based highlighted in red, PET-based in blue, CSF-based in green) for detection of AD pathological changes in the amyloid cascade hypothesis.
OTHER DEMENTIAS
Regional Patterns - AD versus FTD

FTD - frontal atrophy, MTL asymmetrical atrophy most severe in anterior part

AD - more severe MTL/hippocampal atrophy, equally affected MTL on both sides

Mesial Temporal lobe/Hippocampal atrophy
- not specific for AD, even greater in some cases of semantic dementia
- Ectorhinal Cortex volume loss similar in FTD and AD

Frontotemporal Lobar degeneration (FTLD)

Clinical Subtypes:

Frontotemporal dementia (FTD)
Semantic dementia (SD)
Nonfluent aphasia (NFA)

Frontotemporal dementia (FTD) with extrapyramidal symptoms
- Corticobasal degeneration
- Progressive supranuclear palsy

Frontotemporal dementia (FTD) with motor neuron disease
Atrophy patterns for discrimination of FTLD subtypes

Classification based on:
1. Frontal versus Temporal
2. Right versus Left

FTD- bilateral frontotemporal, R>L
SD- predominantly temporal
NFA- bilateral frontotemporal, R<L
Cerebral amyloid angiography (CAA)

- vascular disease associated with recurrent hemorrhagic stroke
- presentation depending on the severity, and might not be diagnosed until autopsy
- autopsy studies show moderate to severe CAA with an age-dependent prevalence of 8% (age 75 to 84) to 12% (age of 84) and has a higher prevalence in patients with Alzheimer's disease (Ellis 1996-25%)
- manifest as β-amyloid protein deposits in small arterioles
- unrelated to systemic amyloidosis, associated with increasing age, dementia, dementia pugilistica, Alzheimer's disease, post-irradiation necrosis and spongiform encephalopathies

Haacke AJNR 2007
Progressive Supranuclear Palsy