Imaging in Dementia: Options for Clinical Practice 2017

John A. Bertelson, MD

Clinical Chief of Neurology, Seton Brain and Spine Institute
Assistant Professor of Medicine, Dell Medical School, UT Austin
Clinical Assistant Professor of Psychology, UT Austin
Disclosures

- None
Outline

- Early Imaging
- Indications for Imaging in Dementia
- Imaging of Alzheimer’s Disease
- Imaging of Other Dementing Disorders
- Future Directions
Early Dementia Imaging - Pneumoencephalography

- Initially described in 1918
- Low resolution
- High morbidity, including:
  - Meningeal irritation, 6 hrs:
    - Headache
    - Nausea
    - Emesis
  - Elevation in BP
- Became obsolete in 1971

1: AJNR 2012
2: http://www.isradiology.org/tropical_deseases/tmcr/chapter45/imaging.htm
Modern Imaging
Traditional Role for Neuroimaging in Dementia

- **Indication:** Rule out reversible process

- Quality Standards Subcommittee of the AAN, 1994:
  - “Neuroimaging should be considered in every patient with dementia”
  - “… potentially treatable disorders that can otherwise be missed, such as tumors, subdural hematomas, hydrocephalus, and strokes.”
  - “… there is no consensus on the need for such studies in the evaluation of patients with the insidious onset of dementia after age 60 without focal signs or symptoms, seizures, or gait disturbances.”

Alter M, 1994
# Evolution of Indications for Neuroimaging in Dementia

<table>
<thead>
<tr>
<th>Entity</th>
<th>Year</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN</td>
<td>1994</td>
<td>Neuroimaging is not routinely recommended</td>
</tr>
<tr>
<td>CCCD</td>
<td>1999</td>
<td>Neuroimaging (head CT) is recommended only in select situations</td>
</tr>
<tr>
<td>AAN</td>
<td>2001</td>
<td>Structural neuroimaging (noncontrast CT or MRI) is appropriate in the routine initial evaluation of patients with dementia</td>
</tr>
<tr>
<td>EFNS</td>
<td>2007</td>
<td>Structural imaging is recommended in every patient suspected of dementia:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Noncontrast CT can identify surgically treatable lesions and vascular disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- To increase specificity, MRI should be used.</td>
</tr>
<tr>
<td>EFNS</td>
<td>2012</td>
<td>Structural imaging (CT or MRI) is recommended in the routine evaluation of every patient with dementia, to exclude secondary causes of dementia.</td>
</tr>
</tbody>
</table>

Key: AAN: American Academy of Neurology  
CCD: Canadian Consensus Conference on Dementia  
EFNS: European Federation of Neurological Subspecialties  

From: Bertelson and Ajtai, 2014
Reversible Causes of Dementia
Copenhagen Memory Clinic

Potentially reversible etiologies for cognitive symptoms
In 1000 memory clinic patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients with potentially reversible causes (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>98</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>34</td>
</tr>
<tr>
<td>Alcohol dependence syndrome</td>
<td>19</td>
</tr>
<tr>
<td>Space-occupying lesions</td>
<td>8</td>
</tr>
<tr>
<td>Metabolic diseases</td>
<td>8</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>7</td>
</tr>
<tr>
<td>Post-traumatic syndromes</td>
<td>6</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>4</td>
</tr>
<tr>
<td>Delirium</td>
<td>1</td>
</tr>
</tbody>
</table>

4-5%

Hejl A 2002
Neuroimaging in Dementia
Alzheimer’s Disease (AD)
Alzheimer’s Disease

- The most common cause of dementia
- Affects over 5 million Americans
- 6th leading cause of death for people in the US
- Affects 1 in 9 age 65 and older, 1 in 3 over age 85
- About 10% of people have early onset which affects people under age 65
Histopathologic Hallmarks of AD

- Major histopathologic hallmarks include
  - Amyloid-β plaques
  - Neurofibrillary tangles
  - Neuronal and synaptic loss

AP = amyloid plaques.
NFT = neurofibrillary tangles.
Courtesy of Albert Enz, PhD, Novartis Pharmaceuticals Corporation.
Model of the Dynamic Biomarkers of Alzheimer’s Disease

Sperling RA, 2011
NIA-AA Diagnostic Criteria for Dementia due to Alzheimer’s Disease

- Probable AD dementia
  - w/ evidence of the AD pathophysiological process

- Possible AD dementia
  - w/ evidence of the AD pathophysiological process

- Pathophysiologically proved AD dementia

- Dementia unlikely to be due to AD

Biomarker

“To improve the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process”

McKhann GM, 2011
AD Imaging Biomarkers

- **Brain Aβ amyloidosis**
  - PIB/florbetapir-PET

- **Brain Tau Deposition**
  - Tau tracer-PET

- **Neuronal injury**
  - FDG-PET

- **MRI atrophy**
  - Medial temporal lobes
  - Paralimbic
  - Temporoparietal cortex
MRI and AD
Posterior Cortical Atrophy (PCA)

- Variant of AD
- Visuospatial impairment
- Prominent atrophy of parietal and occipital cortex
Automated volumetric MRI analysis

- **Hippocampal Volume Eval.**
  - **NeuroQuant®, CorTechs Labs**
  - Commercially available
  - **Reported:**
    - Volumes of hippocampi (HV) and inferior lateral ventricle (ILV)
    - Volumes as % of intracranial volume
    - Normative %, based on age and gender
Volumetric MRI Analysis - NeuroQuant®

PATIENT INFORMATION

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>005_S_0221</th>
<th>Patient Name:</th>
<th>Smith, John Jr.</th>
<th>Sex:</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accession Number:</td>
<td>093951_1</td>
<td>Referring Physician:</td>
<td>Jones, Steven MD, PhD</td>
<td>Exam Date:</td>
<td>2006/02/22 10:18:17 AM</td>
</tr>
</tbody>
</table>

MORPHOMETRY RESULTS

<table>
<thead>
<tr>
<th>Brain Structure</th>
<th>Volume (cm³)</th>
<th>% of ICV (5% - 95% Normative Percentile)</th>
<th>Normative Percentile*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampi</td>
<td>5.93</td>
<td>0.35 (0.43-0.59)</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Lateral Ventricles</td>
<td>56.22</td>
<td>3.35 (0.57-3.64)</td>
<td>93</td>
</tr>
<tr>
<td>Inferior Lateral Ventricles</td>
<td>4.84</td>
<td>0.29 (0.08-0.26)</td>
<td>97</td>
</tr>
</tbody>
</table>
AGE-MATCHED REFERENCE CHARTS*

L & R Hippocampus

L & R Inferior Lateral Ventricle

http://www.cortechs.net/products/neuroquant.php
PET and AD

- FDG PET
- Amyloid PET
- Tau PET
FDG PET
Medicare Guidelines in Dementia

- Effective 9/15/2004,

- “An FDG PET scan is considered reasonable and necessary in patients with:
  - a recent diagnosis of dementia,
  - documented cognitive decline of at least 6 months,
  - meet diagnostic criteria for both AD and FTD.”

FDG PET
Medicare Guidelines in Dementia

- Additional prerequisites include:
  - Comprehensive evaluation already completed, including brain CT or MRI
  - Evaluation by “a physician experienced in the diagnosis and assessment of dementia”
  - Evaluation is indeterminate and FDG PET is reasonably expected to clarify the diagnosis between FTD and AD
  - SPECT or PET have not already been obtained in the past 12 months AND significant clinical changes have occurred
FDG PET

- AD
- FTD
  - PPA
Pittsburgh Compound-B (PIB)

- Radiolabeled thioflavin derivative
- $[N\text{-methyl-(11)C}]2-(4'\text{-methylaminophenyl})-6$-hydroxybenzothiazole
- Selectively binds to amyloid plaque and cerebrovascular amyloid
- Significant retention seen in:
  - 90+% AD patients
  - 60% patients with MCI
  - 30% “normal” elderly
- Very short half life: 20 minutes

Amyloid PET Imaging
Pittsburgh Compound-B PET
Amyloid-binding Radionucleotides

- Florbetapir (*Amyvid*) ¹
  - Marketed in US by Eli Lilly
  - Approved by FDA, not covered by CMS for routine use ²
  - Half life 110 minutes

- Additional FDA-approved radionucleotides ³
  - Florbetaben (*Neuraceq*, Piramal Imaging)
  - Flutemetamol (*Vizamyl*, GE Healthcare)

¹: Florbetapir, package insert
²: CMS Memo (CAG-00431N)
³: Alzforum, downloaded 8.5.14
Tau vs. Aβ Imaging
Human postmortem studies have shown that it is the density of NFTs and not of Aβ insoluble plaques that strongly correlates with neurodegeneration and cognitive deficits.

PET imaging studies suggest that tau deposition more closely correlates with cognition than Aβ deposition.

1. Villemagne 2014
Tau in the Brain

- Phosphoprotein
  - 6 isoforms

- Stabilizes microtubules
  - Cytoskeletal support
  - Intracellular transport (organelles, neurotransmitters, etc)

- Associated with AD, PSP, CBGD, CTE, and several variants of FTD.
Tau PET Tracers

- Ideal tau PET tracer
  - High affinity for phosphorolated tau and neurofibrillary tangles
  - Weak affinity for tau monomers and amyloid

- 7+ tau tracers developed
  - (F-18)T807 in phase 2 trials
Tau PET: (F-18) T807

A. Normal

B. AD
Frontotemporal Degeneration (FTD)
Frontotemporal Dementia Subtypes

- Behavioral variant (bvFTD)

- Language variant (Primary Progressive Aphasia, PPA)
  - Nonfluent/agrammatic
  - Semantic
  - Logopenic

Gorno-Tempini 2011
Radiologist Diagnosis of FTD with MRI

- Review of cases of fronto-temporal dementia with brain MRI

- General radiologists only considered Pick’s disease or bvFTD in 10% of cases

- Neuroradiologists considered these diagnoses in 60% of cases

<table>
<thead>
<tr>
<th>Reported diagnosis</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophy</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Unremarkable</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>White matter/ischemic</td>
<td>6 (15)</td>
</tr>
<tr>
<td>bvFTD</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Alzheimer disease vs Pick disease</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus/hydrocephalus</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Encephalomalacia</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Mitochondrial/metabolic</td>
<td>1 (2.5)</td>
</tr>
</tbody>
</table>

Suarez 2009
Imaging Findings in FTD

- **MRI**
  - Early: “Normal” or focal frontal, insular, or temporal atrophy
  - Late: Progressive focal atrophy (usually bilateral) or generalized atrophy

- **FDG PET**
  - Early: Hypometabolism in the frontal or temporal regions
  - Late: Generalized hypometabolism

- **Amyloid PET**
  - All stages: No significant binding
Progressive Cognitive Decline

T=0 years

T=3 years

T=8 years
Progressive Cognitive Decline

T=0 years

T=3 years

T=8 years

PPA
RRP
IHO
MGAR
RESIVE

A

B

C

*
Tau PET Imaging in FTD variant:

$^{18}$F-AV-1451 (Tau) PET

A-C: 3 patients with MAPT mutation
D: normal control

Smith and Puschmann, 2016
Tau PET Imaging in FTD variant:
Inverse Relationship between Tau and FDG PET

Smith and Puschmann, 2016
Imaging of Other Dementing Disorders
Huntington’s Disease

From: Bertelson and Ajtai, 2014
Progressive Supranuclear Palsy

<table>
<thead>
<tr>
<th>Atrophic midbrain</th>
<th>Normal midbrain</th>
<th>Reduced AP midbrain diameter</th>
</tr>
</thead>
</table>

From: Bertelson and Ajtai, 2014
Multiple System Atrophy

http://radiopaedia.org/articles/multiple-system-atrophy
Multiple System Atrophy

From: Bertelson and Ajtai, 2014
Prion Diseases
sCJD

A
DWI hyperintense caudate and putamen

B and C
DWI hyperintense cortical ribbon

From: Bertelson and Ajtai, 2014
Variant Creutzfeldt-Jakob Disease (vCJD)

- “Hockey stick” sign
- DWI hyperintensity in the bilateral medial thalami and pulvinar

From: Bertelson and Ajtai, 2014
What’s next??

- Wider utilization of neuroimaging biomarkers to:
  - Clarify the diagnosis
    - Alzheimer’s Disease vs. Non-Alzheimer’s Dementias
  - Monitor response to disease modifying agents

- Limitations
  - Cost
  - Access to advanced imaging
  - Inadequacy of response to disease modifying agents
Clinical, genetic, and pathological spectrum of misfolded proteins in neurodegenerative disease

Villemagne 2015
Thank You
References


References


References


References


References


