Brain imaging for the diagnosis of people with suspected dementia

Why do we undertake brain imaging in dementia?
- Not just because guidelines tell us to!
- Exclude other causes for dementia
- Help confirm diagnosis
- Provide reassurance and understanding
- Research

NINCDS/ADRSA Criteria for AD
- Dementia (2 or more cognitive deficits)
- Memory (new learning) impairment
- Impairment in social/ occupational functioning
- Progressive deterioration
- No disturbances of consciousness
- Onset 40-90
- Not accounted for by another brain disorder

McKhann et al, 1984

What is available for clinical imaging in Dementia in 2015?
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Perfusion (HMPAO) SPECT
- Glucose (FDG) PET
- Dopamine (FP-CIT) SPECT (for Lewy body dementia)
- Amyloid (florbetapir) PET

NINDS Neuroimaging Criteria for VaD
- Topography
  - Large vessel strokes
  - Extensive white matter change
  - Lacunes (frontal/basal ganglia)
  - Bilateral thalamic lesions
- Severity
  - Large vessel lesion of dominant hemisphere
  - Bilateral strokes
  - WML affecting >25% white matter

Roman et al, 1993
Control AD Sens for AD around 80%, spec for controls 80%, Spec lower for other dementias (esp FTD) Strongest pathological correlate is tau/ tangle pathology

Control AD Sens for AD around 80%, spec for controls 80%, Spec lower for other dementias (esp FTD) Strongest pathological correlate is tau/ tangle pathology

Structural MR imaging in AD and DLB

Hippocampal atrophy in 100% AD, 62% DLB, 4% controls
42% volume decrease in AD (p<0.001), 14% in DLB (P<0.05)


Baseline

Year 1

2.3% volume loss over 12 months

Difference
Serial MR Imaging in AD and DLB

Mak et al, Neuroimage Clinical, 2015

Blood flow SPECT images (Tc-HMPAO)

Con  AD  FTD  DLB

Sens for AD 65-85%, spec 72-87% for other dementias
Similar changes seen with FDG PET
FDG PET may have higher sensitivity (75-99%) but few direct comparisons

Davidson and O'Brien. In J Ger Psych 2013

What is the difference between these two scans?

CFD PET scan of control
HMPAO SPECT scan of same control

SUSPECTED-AD study

A Study of the clinical Utility, patient preference and cost benefit of SPECT and PET-CT brain imaging in the Evaluation and Diagnosis of Alzheimer’s Disease

Are perfusion (HMPAO) SPECT and FDG PET equally useful in the differential diagnosis of degenerative dementia?

NIHR funded

Aims

• To undertake a direct comparative study of the utility of perfusion (HMPAO) SPECT and FDG-PET for:
  • The differential diagnosis of degenerative dementia (AD & DLB; n=68) from similarly aged healthy controls (n=30)
  • Sub-type differentiation of AD (n=38) from DLB (n=30)

• Our hypothesis was that FDG-PET would be significantly superior to HMPAO SPECT
Methods (I)

- 102 subjects, 3 did not undergo both scans, 1 scan excluded technically
- 30 Probable DLB
- 38 Probable AD
- 30 similar aged controls
- Consensus clinician diagnosis was the “standard of truth” (acceptable standard in absence of autopsy)

Methods (II)

- Full clinical, cognitive, motor and neuropsychiatric assessment
- SPECT and PET in balanced order
- SPECT: 500 MBq Tc-HMPAO, Siemens Symbia S dual gamma camera, 30 min scan
- PET: 250 MBq F-18 FDG, Siemens Biograph Truepoint PET-CT, 10 min scan
- CT not used for ratings to avoid bias to PET

Subject demographics

<table>
<thead>
<tr>
<th></th>
<th>Control (N=30)</th>
<th>AD (N=38)</th>
<th>DLB (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.3 (6.6)</td>
<td>75.8 (7.5)</td>
<td>76.5 (5.8)</td>
</tr>
<tr>
<td>Female/Male</td>
<td>10/20</td>
<td>16/22</td>
<td>7/23</td>
</tr>
<tr>
<td>Duration of dementia (months)</td>
<td>44 (23)</td>
<td>38 (27)</td>
<td>ns</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.9 (1.1)</td>
<td>20.9 (3.7)</td>
<td>21.8 (4.2)</td>
</tr>
<tr>
<td>CAMCOG</td>
<td>98.4 (4.0)</td>
<td>71.9 (12)</td>
<td>73.6 (13)</td>
</tr>
<tr>
<td>Rey total</td>
<td>70.3 (12)</td>
<td>25.6 (10)</td>
<td>33.4 (12)</td>
</tr>
<tr>
<td>CAF total</td>
<td>1.8 (1.8)</td>
<td>4.5 (2.7)</td>
<td>8.1 (3.8)</td>
</tr>
<tr>
<td>NPI total</td>
<td>2.6 (2.7)</td>
<td>15.6 (15)</td>
<td>19.7 (16)</td>
</tr>
<tr>
<td>UPDRS</td>
<td>3.3 (3.2)</td>
<td>5.5 (6.6)</td>
<td>8.2 (12)</td>
</tr>
<tr>
<td>UPDRS to MMSE</td>
<td>0.7 (1.8)</td>
<td>1.9 (2.2)</td>
<td>3.7 (3.3)</td>
</tr>
</tbody>
</table>

AD v DLB: ns

PET-CT of AD subject

PET vs SPECT

Consensus visual rating diagnosis

<table>
<thead>
<tr>
<th></th>
<th>FOG-PET</th>
<th>SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>AD</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>DLB</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

PET:
- Sensitivity 85%
- Specificity 90%
- AD vs DLB:
- Sensitivity 74%
- Specificity 70%

*p <0.05
ROC Curves

AUC: PET = 0.93, SPECT = 0.72, p = 0.001
AUC: PET = 0.80, SPECT = 0.58, p = 0.005

SPM analysis

SPM t statistic AD > DLB
PET
SPECT


Voxel based analysis: number of significant voxels out of total (261253)

<table>
<thead>
<tr>
<th></th>
<th>FDG-PET</th>
<th>HMPAO SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>156019</td>
<td>62802</td>
</tr>
<tr>
<td>Dementia</td>
<td>64747</td>
<td>1561</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FDG-PET</th>
<th>HMPAO SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12533</td>
<td>3594</td>
</tr>
<tr>
<td>Dementia</td>
<td>7001</td>
<td>1554</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FDG-PET</th>
<th>HMPAO SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>7427</td>
<td>1554</td>
</tr>
<tr>
<td>Dementia</td>
<td>4413</td>
<td>1554</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FDG-PET</th>
<th>HMPAO SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>17580</td>
<td>232</td>
</tr>
<tr>
<td>Dementia</td>
<td>7932</td>
<td>232</td>
</tr>
</tbody>
</table>

Dopaminergic imaging, a biomarker for Lewy body dementia

- Phase 2 study of diagnosis (DLB v AD). Sens 78% Spec 90%
- Phase 3 Study (GE Healthcare funded). Similar diagnosis accuracy in 40 sites
- Autopsy validation
- Licensed for clinical use in dementia in EU (2006)

NICE/SCIE Guidelines for Dementia (2006)

- Structural imaging should be used to exclude other cerebral pathologies and to help establish the subtype diagnosis
- HMPAO SPECT should be used to help differentiate between AD, VaD and FTD if the diagnosis is in doubt. FDG PET may be used if HMPAO SPECT is not available
- FP-CIT SPECT should be used to help establish the diagnosis of DLB if the diagnosis is in doubt

NICE/SCIE Guidelines for Dementia (20??)

- Structural imaging should be used to exclude other cerebral pathologies and to help establish the subtype diagnosis
- FDG PET should be used to help differentiate between AD and other dementias if the diagnosis is in doubt. HMPAO SPECT may be used if FDG-PET is not available
- FP-CIT SPECT should be used to help establish the diagnosis of DLB if the diagnosis is in doubt


Amyloid imaging in Dementia

Villemagne et al, 2011

PIB – research tool
Now F-amyloid compounds for clinical use

• Use in highly selected patients where:
  • Alzheimer’s dementia (AD) is a possible diagnosis but this remains uncertain after comprehensive evaluation by a dementia expert and conventional imaging work-up, and
  • Knowledge of the presence or absence of amyloid is expected to increase diagnostic certainty and influence patient management
• Appropriate uses: unexplained dementia, unusual clinical presentation, very young age of onset
• Inappropriate uses: established AD, in those with no cognitive impairment or as a screening test

Evidence-based indications for PET-CT: 18F-Florbetapir

November 2013

Relationship between AD biomarkers (?)


AD Criteria are on the move

Gradual and progressive change in memory function reported by patients or an informant over more than 6 months
• Objective evidence of significantly impaired episodic memory
  Plus at least one of:
  • Medial temporal lobe atrophy on MR
  • Bilateral temporal/parietal hypometabolism on PET/SPECT
  • Amyloid positive PET imaging
  • Abnormal CSF biomarkers (reduced A beta 42, raised tau / p-tau)

Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria


International Working Group (IWG)

Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA criteria


International Working Group (IWG)

Novel PET markers of Tau

What scan to do……..

• Don’t panic! Or get left behind……..
• Be aware of what is available locally – make some new friends
• Basic dementia assessment: CT or MRI. Investigate possibility of “coronal CT”
• Use MRI if suspect vascular pathology (not seen on CT) or “funny” dementia
• If uncertainty remains consider FDG PET (organic v non-organic; AD v FTD) or dopaminergic (DLB) SPECT
• Diagnostic puzzle/ odd case with reasonable likelihood of AD diagnosis, consider amyloid PET (esp if young)

Thank you!