FUNCTIONAL IMAGING IN NEURODEGENERATIVE DISORDERS

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INTRODUCTION

- Neurodegenerative disorders of the CNS (dementias, movement disorders) is one of the major medical, social and financial problem in developed countries.
- Increase of manifestation is matching with increase of life expectancy.
- Genetic, functional and metabolic predisposition is a challenge for the development of novel regimens.
INTRODUCTION

- Alzheimer’s disease (60-65%)
- Lewy-body dementia (20-25%)
- Multi-infarct dementia (10-15%)
- Fronto-temporal dementia
- Mixed dementia
- Parkinson’s disease
- Creutzfeldt-Jacob’s disease
- Parkinson-plus syndromes.
DIAGNOSIS

- Clinical evaluation
- Neuro-psychological tests (MMSE, CAMCOG)
- Blood and/or urine smears for the estimation of “curable” dementias.
COMPUTERIZED TOMOGRAPHY

• Useful for excluding causes of dementia other than Alzheimer's disease.
• May show general or regionalised atrophy, white matter changes, space-occupying lesions, and vascular disease.
• Permits detection of hippocampal atrophy, which may be specific for Alzheimer's disease.

Limitations:
• Inability to distinguish grey and white matter.
• May miss old haemorrhage.
• Useful only in moderate or advanced dementia.
• Poor capability in differential diagnosis.
CT level 2 for regional atrophy: linear measurements of medial temporal lobe atrophy based on CT films. Minimum thickness of the medial temporal lobe: the measurement is taken in the parahippocampal gyrus region where the portion between the anterior and posterior aspects of the brainstem is thinnest (white arrows). Radial width of the temporal horn: the measurement is the distance between two parallel lines drawn tangential to the tip of the temporal horns where its width is maximum (red arrows). Right side, non-demented elderly person; left side: Alzheimer's disease.

Frisoni, G B et al. J Neurol Neurosurg Psychiatry 2003;74:1371-1381
MAGNETIC RESONANCE IMAGING

**Advantages:**

- Allows assessment of grey and white matter bulk; and global and regional volume.
- More accurate assessment of the morphological features of hydrocephalus.
- Ability to image small lacunar strokes and posterior fossa lesions.
- Superior to CT in imaging subacute haemorrhage.
- Permits direct visualisation of hippocampal formation.

**Disadvantages:**

- Contraindicated in patients with metallic implants.
- Relative contraindications (claustrophobic, anxious patients).
- Limited availability and high expense.
High resolution MRI is capable to discriminate normal subjects from demented ones, based on hippocampal atrophy with a sensitivity of 80% and a specificity of 75%, but the mean MMSE of pts was at the level of 15.

Erkinjutti T et al. J Neurol Neurosurg Psych 1988, 51:1037-44
Brain Imaging in Clinical Practice

- **Clinical Radiology**
  - Instrumentation induces signal changes and detects the effects

- **Nuclear Medicine**
  - The radioligand is the source of the signal
  - Instrumentation detects the signal
Functional Specificity is Characteristic of Brain Emission Tomography
STATISTICAL PARAMETRIC MAPPING OF BRAIN PERFUSION
MILD COGNITIVE IMPAIRMENT (MCI)

- Individuals not fulfilling the criteria of AD, but “expressing a subgroup” of high risk.
- SPECT & PET: reduction of rCBF and glucose metabolism, respectively, at the posterior cingulate gyrus and precuneous region.
- Fluctuations of blood flow and metabolism:
  - In males: ↓blood flow at the posterior parietal cortex plus precuneous region.
  - In females: ↓blood flow at the medial aspect of temporal plus at the frontal cortex.
The significance of memory complaints in subjects who do not yet match the criteria for AD but who are at high risk of developing a full-blown dementia syndrome in the next few years has recently attracted attention. This at-risk state is commonly referred to as mild cognitive impairment (MCI).

Many researchers have demonstrated metabolic and blood flow reductions in the parietotemporal association cortex. This finding has been widely recognized as a diagnostic pattern for AD. The parietotemporal involvement is bilateral, although asymmetry in the degree of perfusion or metabolic reduction is recognized. Thus, it has been reported consistently that the posterior association cortex is the first cortical region to be affected in AD. The deficit spreads to the frontal lobes as the disease progresses, with persisting asymmetry.

In amnestic MCI, a decrease in rCBF as well as glucose metabolism in the posterior cingulate gyrus and precuneus has been observed with PET/SPECT.

Petersen RC et al Arch Neurol 2001
Kemp PM et al J Neurol Neurosurg Psychiatry 2003
Predementia stage (CDR 0.5)  Moderate AD (CDR 2)  Severe AD (CDR 3)
rCBF SPECT z scores:
pre treatment with donepezil
Preclinical Evidence of Alzheimer's Disease in Persons Homozygous for the (epsilon)4 Allele for Apolipoprotein E

Regions of the Brain with Reduced Rates of Glucose Metabolism in 11 (epsilon)4 Homozygotes and Their Relation to Brain Regions with Reduced FDG in 37 Patients with Probable AD.

**Purple areas** - significantly reduced FDG only in the group with probable AD.

**Blue areas** – significantly reduced FDG in both the (epsilon)4 homozygotes and patients with probable AD.

**Green areas** – significantly reduced FDG only in the (epsilon)4 homozygotes - significantly reduced rates of glucose metabolism bilaterally in the posterior cingulate (PC), parietal, temporal, and prefrontal (PF1) regions as the patients with probable AD, as well as in additional prefrontal (PF2) regions (? accelerated aging in this group).

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<th>MMS</th>
<th>CAMCOG Battery</th>
<th>Memory recall</th>
<th>Perception and orientation</th>
<th>Calculation</th>
<th>Praxis</th>
<th>Aphasia</th>
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MOLECULAR (PET) STUDY

- [18F] 1,1-dicyano-2-[6-(dimethylamino)-2-naphtalenyl] propene (18F-FDDNP)
- 2-N-methyl-C11-(4′-methylaminophenyl)-6-hydroxy-benzothiasole (11C-PIB)
- 4-N-methylamino-4′-hydroxystilbene (11C-SB13)
Pittsburgh compound B (N-methyl-[11C]2-(4-methylaminophenyl)-6-hydroxybenzothiazole)-[11C]PIB
Future Diagnosis And Treatment of AD

- In the future effective treatments for AD may be available, and with effective treatment will come increasing demand for brain SPECT, FDG-PET and b-amyloid-PET.

- Persons at risk for AD, including those with subjective memory complaints, ApoE-ε4 carriers, those with a family history of AD, or individuals showing decline on cognitive testing, will require further investigation.

- If positive, treatment to reduce b-amyloids could be initiated well before dementia has developed.
Effect on cerebral metabolism assessed with FDG PET of antibody therapies for AD FDG PET at baseline and 6 mo after initiation of intravenous immunoglobulin treatment or after placebo.

Less decline in glucose metabolism in the medial temporal regions in those under treatment than in those on placebo.

*J Nucl Med 2011, 10: 22-28N.*
OPTIMA STUDY
(Oxford Project to Investigate Memory in Aging)

- Clinical diagnosis: -sensitivity 59%
  -specificity 95%

- Combination of functional SPECT study and clinical criteria: -sensitivity 93%
  -specificity 85%

Diagnostic accuracy of FDG-PET in AD

Effectiveness and Safety of $^{18}$F-FDG PET in the Evaluation of Dementia: A Review of the Recent Literature
Nicolaas I. Bohnen1,3, David S.W. Djang4, Karl Herholz5, Yoshimi Anzai6, and Satoshi Minoshima5

**$^{18}$F-FDG PET Diagnosis of AD in Cross-Sectional Case-Control Studies**

<table>
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<tr>
<th>Reference</th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
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<td>AD</td>
<td>Healthy control</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>100%</td>
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<td>AD</td>
<td>Healthy control</td>
<td>12</td>
<td>3</td>
<td>10</td>
<td>15</td>
<td>80%</td>
<td>60%</td>
<td>68%</td>
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<td>Healthy control</td>
<td>47</td>
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<td>9</td>
<td>51</td>
<td>90%</td>
<td>85%</td>
<td>88%</td>
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<tr>
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<td>Healthy control</td>
<td>192</td>
<td>2</td>
<td>2</td>
<td>108</td>
<td>99%</td>
<td>98%</td>
<td>99%</td>
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<td>McMurry et al., 2008 (90)</td>
<td>AD</td>
<td>Elderly control with only subjective memory complaints</td>
<td>25</td>
<td>2</td>
<td>4</td>
<td>23</td>
<td>93%</td>
<td>85%</td>
<td>89%</td>
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<td><strong>Total</strong></td>
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<td>309</td>
<td>12</td>
<td>25</td>
<td>216</td>
<td><strong>96%</strong></td>
<td><strong>90%</strong></td>
<td><strong>93%</strong></td>
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FN = false-negative; FP = false-positive; TN = true-negative; TP = true-positive.
FDG/PET and IBVM/SPE(C)T in AD-SPM analysis

[\textsuperscript{123}I]iodobenzovesamicol (IBVM) as an in vivo measure of cholinergic neuronal integrity.

Ann Neurol 1996 Sep; 40(3): 399-410
- Binding in controls (22 - 91 y) declines 3.7% per decade.
- Inverse correlation with dementia severity in AD.
- Early onset AD (< 65 y) severely reduced binding throughout entire cerebral cortex and hippocampus (about 30%).
Major Depressive Disorder

Bilateral frontal hypoperfusion is the most frequently reported finding.

Possible parietal and less frequently temporal hypoperfusion.

Improvement with successful response to therapy.
Lewy-body dementia

- Temporoparietal hypoperfusion on rCBF-SPECT is common to both AD and DLB. Occipital hypoperfusion is more frequently seen in DLB.

- Although not diagnostically specific in individual cases, occipital hypoperfusion on rCBF-SPECT should raise suspicion that DLB may be the cause of dementia, prompting careful search for other features of the disorder.

Lobotesis K et al Neurology 2000, 56: 643-49.
KJ, 67 y old male; no previous psychiatric history; onset at 55 y; persistent visual hallucinations; tremor; rigidity and akinesia H &Y=3.0; MMSE=unable; CAMCOG=unable; CDR=3.0

- DaTSCAN
- CN and putamen demonstrated; low background
- R CN=5.79  L CN=5.72
- R AP=4.92  L AP=5.04
- R PP=3.66  L PP=4.28

- Neuropathological diagnosis:
  - Alzheimer’s disease;
  - neuritic plaques
  - neurofibrillary tangles;
  - no Lewy bodies; no nigral degeneration
LW, 84 y old male; FH of PD and AD; no past psychiatric history; acute confusional state; vis. hallucin; no tremor; falls; fluctuation

H&Y=1.0; UPDRS=2.0; MMSE=18; CAMCOG=76

- DaTSCAN
- CN demonstrated bilaterally;
- putamen left > right; high background
- R CN=3.55  L CN=3.49
- R AP=2.57  L AP=3.02
- R PP=2.18  L PP=2.45

- Neuropathological diagnosis:
- Dementia with Lewy bodies;
- Cerad 4a;
- Braake stage 2; CLB score 8;
- severe nigral degeneration.
- DaTSCAN cannot differentiate between DLB and Parkinson’s disease dementia as they share the same underlying LB pathology.

- It has been postulated that these two entities may represent ends of the same clinical spectrum, with an arbitrary dividing line between cases in which dementia develops within 1 year of onset of clinical parkinsonism, classified as DLB, and cases in which dementia develops later, classified as Parkinson’s disease dementia.
Cortico-Basal Degeneration

- Hypoperfusion in several cortical areas, mostly the parietal cortex. Less frequently there is frontal and temporal involvement.
- Hypoperfusion in the basal ganglia.
- Unilateral or Bilateral and Asymmetrical
Pick’s Disease
Frontal Lobe Dementia

Anatomo-pathology (frontal cortex atrophy)
Brain perfusion SPE(C)T (frontal lobe hypoperfusion)
PET απεικόνιση με F-18-FDG στις άνοιες

NORMAL AGING

ALZHEIMER’S

PICK’S
VASCULAR DEMENTIA

- Alzheimer's disease can be easily differentiated from vascular dementia with the Tc-99m-HMPAO SPECT study. The pattern in cases of VD is that of multiple segmental or subsegmental defects of perfusion spared throughout the cortex and in the subcortical areas.

- In cases of "mixed dementia" the acetazolamide test can differentiate pts with DAT, because in these cases the vasodilatory capacity of the brain capillary blood vessels is maintained.
Creutzfeldt-Jacob Encephalopathy
CONCLUSIONS-TARGETS

- Early diagnosis and evaluation of MCI
- Differential diagnosis
- Diagnosis based on cellular and genetic level
- Efficacy of therapeutic regimens
- Pre-clinical diagnosis?
ΜΟΛΩΝ ΛΑΒΕ = COME AND GET IT!