Role of CT, MRI, SPECT and PET in Alzheimer Disease

August 12, 2017  9:00 to 10:00 AM

Fernando Zalduondo Dubner, MD
Diplomate ABR, Fellow ACR
fzalduondo@spmedflix.com

Ponce School of Medicine Symposium

e mail me and I will send two articles
Brain PET in Suspected Dementia: Patterns of Altered FDG Metabolism

Richard K. J. Brown, MD
Nicola M. Bolloon, MD, PhD
Ko K. Song, MBBS
Satkuru Muralidhar, MD, PhD
Kirk A. Frey, MD, PhD

The diagnosis of dementia syndromes can be challenging for clinicians, particularly in the early stages of disease. Patients with higher education levels may experience a marked decline in cognitive function before their dementia is detectable with routine testing methods. In addition, comorbid conditions (e.g., depression) and the use of certain medications can confound the clinical assessment. Clinicians require a high degree of certainty before making a diagnosis of Alzheimer disease or some other neurodegenerative disorder, since the impact on patients and their families can be devastating. Moreover, accurate diagnosis is important because emerging therapeutic regimens vary depending on the cause of the dementia. Clinically based testing is useful; however, the results usually do not enable the clinician to make a definitive diagnosis. For this reason, imaging biomarkers are playing an increasingly important role in the workup of patients with suspected dementia. Positron emission tomography with 2-[fluorine-18]fluoro-2-deoxy-D-glucose allows detection of neurodegenerative disorders earlier than is otherwise possible. Accurate interpretation of these studies requires recognition of typical metabolic patterns caused by dementia and of artifacts introduced by image processing. Although visual interpretation is a vital component of image analysis, computer-assisted diagnostic software has been shown to increase diagnostic accuracy.

Introduction

Early diagnosis and characterization of dementia is a growing challenge in medicine. Primary neurodegenerative disorders are the leading cause of dementia and are characterized by progressive, accumulative damage to neuronal structures and interconnectivity, with clinical consequences of memory loss and progressive impairment of higher cognitive functions, leading to social and occupational dysfunction (1). In the United States, these disorders affect more than 14% of the population over 65 years of age and more than 50% of individuals older than 85 years (2-4). Alzheimer disease is the most common cause of dementia in the elderly and is the fourth leading cause of death in individuals over 65 years of age (1,2,4,5). Other frequently encountered disorders include frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB). Alzheimer disease accounts for 50% - 60% of dementia, with FTD...
Disclosure: Owner and medical director of San Patricio MEDFLIX, a private radiology and nuclear medicine ambulatory imaging center. Dr. Carlos Jiménez Marchán, Director of Nuclear Medicine. No commercial conflicts of interest.
Question  True or False

In the setting of Alzheimer disease.

___ MRI and SPECT-CT are more sensitive than FDG PET-CT.

___ The correct way to request a PET-CT is: “rule out Alzheimer disease.”

___ It is crucial to review all prior cerebral anatomic studies, including CT and MRI scans of the brain, and prior nuclear medicine brain SPECT-CT during the interpretation of FDG PET-CT.

___ Functional nuclear medicine studies may detect findings suggestive of AD before anatomic changes are revealed by radiologic (CT/MRI) studies.
MILD COGNITIVE IMPAIRMENT - MCI

• MCI = incipient dementia = isolated memory impairment

• Considered the boundary or transitional stage between normal aging and dementia.

• Diagnosis:
  – when cognitive impairments are beyond those expected for their age and education, but that do not interfere significantly with their daily activities.

• Most-studied type of MCI involves memory problems, called amnestic MCI, regarded as a risk factor for AD.

Deterioro Cognitivo Leve

DEMENTIA

- Definition - serious loss of cognitive ability in a previously unimpaired person beyond what might be expected from normal aging.
- Dementia - nonspecific illness syndrome affecting areas of cognition:
  - memory
  - attention
  - language
  - problem solving skills.
- Affects > 24 million people worldwide
- >5 million new cases annually.

DEMENTIA

• Required to be present for **at least 6 months** for diagnosis.

• Dementia that begins gradually and **worsens progressively** over several years is usually caused by neurodegenerative disease
  
  - conditions affecting only or primarily the neurons causing gradual but **irreversible loss of function**.

• Most common form is Alzheimer’s Disease.

AGENDA

• The Challenge: Making an Early Diagnosis
  – Clinical and Imaging challenges
  – Imaging the Brain in AD, Approach

• Imaging Modalities
  – Structural /Radiologic
    • Ranking Modalities
  – Functional/Nuclear Medicine
    • Ranking Modalities

• The Bottom Line/Take Home
AGENDA

• The Challenge: Making an Early Diagnosis
  – Clinical and Imaging challenges
  – Imaging the Brain in AD, Approach

• Imaging Modalities
  – Structural /Radiologic
    • Ranking Modalities: Why is MRI better than CT
  – Functional/Nuclear Medicine
    • Ranking Modalities: Why is FDG PET-CT better than SPECT-CT

• The Bottom Line/Take Home
• Clinically:
  – early disease - subtle equivocal signs and symptoms,
  – patients with higher education levels may experience a marked decline in cognitive function before their dementia is detectable with routine testing methods
  – comorbid conditions such as depression and use of certain medications can confound clinical assessment

IMAGING OF THE BRAIN IN AD, APPROACH

• Clinically:

  – clinicians require a highest degree of certainty possible before making the diagnosis of AD or other major neurodegenerative disorder
    • given devastating impact on patient and their family

  – early diagnosis and characterization of dementia is a growing challenge but is crucial given high incidence and aging population, including Puerto Rico’s
    • to guide appropriate therapy
IMAGING OF THE BRAIN IN AD, APPROACH

• Imaging:
  
  – neuroimaging findings are also subtle and often equivocal in early neurodegenerative disease
  
  – it is also challenging for the neuroradiologist and nuclear medicine physician to detect early disease
  
  – structural neuroimaging evaluation is based on nonspecific features such as atrophy, which is a late feature in the progression of the disease.
• Frequently, by the time imaging findings are clear cut, patient has declared clinically, and the diagnosis is either already established or already strongly suggested.

• The true role of imaging is to sway clinicians towards or away from a particular differential rather than making a firm diagnosis.

Dr. Yuranga Weerakkody & Frank Gaillard et al.
CT in AD
MAIN CONDITIONS OF INTEREST

• Although a wide gamut of conditions may fall under the category of *neurodegenerative disease* and even more may result in *mild cognitive impairment*, most fall within a small group:
  – Alzheimer disease (AD) 50-60%
  – Frontotemporal lobar degeneration 15-25%
  – Lewy body disease (LBD) 15-25%

Synchronicity with vascular dementia.

CT and better yet, MRI exclude mimickers:

- Chronic cortical, subcortical and or lacunar infarcts
- Hematoma
  - Subdural
  - Intraaxial
- Tumors, particularly at the anterior and middle cranial fossae
- Severe microvascular ischemic disease which is often synchronous with neurodegenerative disease
- Normal pressure hydrocephalus (N.P.H.)
The neuroradiologist can identify on structural neuroimaging specific findings for these conditions.

- Creutzfeldt-Jakob disease
- Progressive supranuclear palsy (PSP)
- Multi system atrophy (MSA)
- Huntington disease (HD)
- Corticobasal degeneration (CBD)
- CADASIL – cerebral AD arteriopathy with subcortical infarcts and leukoencephalopathy
Radiologist is your colleague

Allow me to help you
Radiologist is your colleague

- We need a good history
- Length of cognitive decline
- Complex partial seizures or other type
- Hypertension, controlled, uncontrolled
- Diabetic, type I vs. II
- Previous documented infarct, distribution and type: cortical, subcortical, lacune
- Parkinson disease or other
Previous imaging studies

It is crucial for the referring physician and for the interpreting imaging specialist, neuroradiologist and nuclear medicine physician, to *serially review all prior cerebral anatomic studies.*
Why previous studies

Imaging specialist needs to ascertain the potential benefit, if any, of the patient from obtaining a functional modality study after review and comparison, before making or deciding to not make recommendation for further imaging.

Avoids false positives in functional studies produced by underlying structural pathology simulating neurodegenerative disease.
Midline posterior cerebellar vs. occipital cortical metabolic defect. Recommend CT or MRI correlation.
Defect represents a retrocerebellar arachnoid cyst. Excluded cortical infarct and Lewy Body disease.

No need for further imaging with PET-CT
Save and bring. Request comparison.

Save and bring.

Demand from patient or family to save the studies and to always take them to the imaging center along with their reports.

Request comparison in your order.

Routinely request your radiologist and nuclear medicine physician in your requisition to compare with previous.
AGENDA

• The Challenge: Making an Early Diagnosis
  – Clinical and Imaging challenges
  – Imaging the Brain in AD, Approach

• Imaging Modalities
  – Structural /Radiologic
    • Ranking Modalities: Why is MRI better than CT
  – Functional/Nuclear Medicine
    • Ranking Modalities: Why is FDG PET-CT better than SPECT-CT

• The Bottom Line/Take Home
IMAGING MODALITIES

STRUCTURAL

• Computerized Tomography – CT
• Magnetic Resonance Imaging – MRI
IMAGING MODALITIES

FUNCTIONAL

- Single Photon Emission Computed Tomography
  SPECT

- Positron Emission Tomography
  PET
FUNCTIONAL

- Single Photon Emission Computed Tomography
  SPECT-CT

- Positron Emission Tomography
  PET-CT
AGENDA

• The Challenge: Making an Early Diagnosis
  – Clinical and Imaging challenges
  – Imaging the Brain in AD, Approach

• Imaging Modalities
  – Structural /Radiologic
    • Ranking Modalities: Why is MRI better than CT
  – Functional/Nuclear Medicine
    • Ranking Modalities: Why is FDG PET-CT better than SPECT-CT

• The Bottom Line/Take Home
STRUCTURAL IMAGING MODALITIES

CT

Map of tissue attenuation by X rays
Look for: Preferential atrophy

MRI

Map of hydrogen protons; radiofrequency waves applied to a static magnetic field
Look for: Preferential atrophy
Disproportionate/Preferential Hippocampal Atrophy

• Atrophy has been shown to correlate with likelihood of progression from mild cognitive impairment to dementia.

• autosomal dominant AD:
  – Hippocampal atrophy may manifest up to 3 years before the clinical onset of mild cognitive impairment.
Temporal lobe

Coronal section. Posterior part

Heschl’s gyrus

Sylvian fissure

Wernicke area

Superior temporal sulcus

Middle temporal gyrus

Inferior temporal sulcus

Inf.temp. gyrus

Alveus

Hippocampus

Dentate

Para hippocampal gyrus

Collateral sulcus

Fusiform gyrus

CA 1

Subiculum
Mesial Temporal Region

Blumenfeld, 2000
CT vs. MRI
CT Strengths

- Widely available
- Much faster than MRI requiring less patient cooperation
- Less expensive than MRI
- Detects calcific atherosclerosis whereas MRI is not sensitive to calcification
CT Weaknesses

- Ionizing radiation - non issue in age group

- X ray beam hardening artifact precludes optimum evaluation of posterior, middle and anterior cranial fossae anatomy

- Less inherent soft tissue contrast - Unreliable definition of hippocampus
CT: X ray beam hardening artifact amalgams, anterior middle and posterior fossae
CT in AD

Cerebral atrophy determined on CT by linear diameters:
• bifrontal
• bicaudate
• third and lateral ventricles
adjusted to skull diameter to account for normal variation

Too much overlap with normal aging patients related atrophy, for which these are unreliable

Moreover, reliable visualization of hippocampi hindered by
• X ray beam hardening artifact
• variable scanner quality and collimation/thickness
CT in AD

Images obtained routinely in the axial plane which is not optimal for optimal visualization of hippocampus.
CT in AD - coronal oblique

On spiral 3D acquisitions, coronal oblique reconstructions orthogonal to the long axis of the hippocampus.

How is it done? Identify the hippocampus off midline in reconstructed parasagittal images.
CT hippocampus, parasagittal
CT cross reference orthogonal to hippocampus
CT coronal oblique, normal hippocampus
CT abnormal hippocampus
CT cross reference orthogonal to hippocampus
CT coronal oblique, abnormally atrophied hippocampus
MRI Strengths

- State of the art magnetic field strength ($T = \text{Tesla}$):
  - 1.5 T and 3.0 T
  - greatest signal = information
  - Gradients performance
  - Crucial in neuroimaging
  - Conventional MRI better than Open
- No ionizing radiation, instead magnetic fields and RF pulses
MRI Strengths

- Better soft tissue contrast
  - More sensitive than CT for gray and white matter disease
  - Hippocampus is gray matter
  - Hippocampal visualization
    - Thin section coronal oblique orthogonal to its long axis are required
    - T2 vs. T1 weighted images
  - Hippocampal architecture
MRI Weaknesses

- Less widely available.
- More expensive.
- Takes longer than CT and requires greater patient cooperation.
- Different types but more numerous types of image artifact than CT.
• **05-22-2011**: 1st patient with a cardiac PM in PR underwent MRI scan safely @ MEDFLIX.

• To date, we have uneventfully scanned over 100 patients with MRI compatible cardiac PM.

• **Advocate routine placement!!**
Not Contraindicated

- Most orthopedic extremity and spine hardware
- Cardiac valves
- Modern aneurysm clips
- Modern Pacemakers
- Most stents and IVC filters
  - Allow 4 - 6 weeks for endothelial anchoring
MRI: Major Contraindications

- **Old** pacemakers*
- **Old** cerebral aneurysm clips**
- Metal in eye – torque, hemorrhage
- Some biomedical implants
  - cochlear
  - middle ear prosthesis
- Some penile implants
- Others
Measuring the Hippocampus

1. Medial temporal lobe atrophy MRI score

**Score of 0 to 4:**
- Lateral ventricle temporal horn width
- Lateral ventricle choroid fissure width
- Hippocampal height
- Interpreted in relation to age:
  - <75 years: ≥2 is abnormal
  - ≥75 years: ≥3 is abnormal

2. Direct volume measurement tracing outline along hippocampus and adding images with software.
MRI – assessing hippocampus

• #2 Medial temporal lobe atrophy MRI score
Visual score from 0 to 4 on MRI, coronal obliques:
  – Choroid fissure width
  – Temporal horn of lateral ventricle width
  – Hippocampal height
Score of 0 to 4 on MRI:

- Interpreted in relation to age:
  - <75 years: ≥2 is abnormal
  - ≥75 years: ≥3 is abnormal

- Four images available for each score.
Medial temporal lobe atrophy MRI score

Score of 0 to 4:

0: no CSF visible around hippocampus

1: choroid fissure slightly widened

2: choroid fissure moderately widened mild enlargement of temporal horn mild loss of hippocampal height
Medial temporal lobe atrophy MRI score

Score of 0 to 4:

3: choroid fissure markedly widened
   moderate enlargement of temporal horn
   moderate loss of hippocampal height

4: choroid fissure markedly widened
   marked enlargement of the temporal horn
   markedly atrophied hippocampus
   internal structure is lost
Measuring the Hippocampus: **Limitations**

1. **Medial temporal lobe atrophy MRI score**
   - Reproducibility requires uniform MR acquisition protocol
   - Scoring is quite subjective: mild, moderate, marked

2. **Direct volume measurement tracing outline along hippocampus and adding images with software**
   - Software not available for all scanner vendors
   - Tedious, time consuming
   - No insurance coverage

None is widely used nor accepted, including our practice.
#1 MRI coronal oblique 3D T1

A  Normal  B  Disproportionately Atrophied Hippocampi
#2 MRI coronal oblique T2

2013 Normal

2017 AD bilateral
#3 MRI axial

2013 RT hipp

2017 progression
#3 MRI coronal

2013 RT hipp

2017 progression RT, new LT
Patient #3  FDG PET

2017 R > L hipp
AGENDA

• The Challenge: Making an Early Diagnosis
  – Clinical and Imaging challenges
  – Imaging the Brain in AD, Approach

• Imaging Modalities
  – Structural /Radiologic
    • Ranking Modalities: Why is MRI better than CT
  – Functional/Nuclear Medicine
    • Ranking Modalities: Why is FDG PET-CT better than SPECT-CT

• The Bottom Line/Take Home
Why is MRI better than CT?

• Better intrinsic resolution than CT

• More reliable and reproducible visualization of hippocampus allows volume estimation

• No X ray beam hardening artifact
CT vs. MRI
MRI much closer than CT
Why is MRI better than CT?

• Increased specificity with Differential Dx

• Atrophy with T2/FLAIR hyperintensity
  – mesial temporal sclerosis (CPSz)

• Enlargement with T2/FLAIR hyperintensity
  – tumor
  – infection (Herpes encephalopathy)
  – vascular lesion (cavernoma, other)
  – other
MRI Specificity in addition to Sensitivity

atrophy + T2 hyperintensity  mesial temporal sclerosis (CPSz)
MRI Specificity in addition to Sensitivity

Tumor Ganglioglioma
AGENDA

- The Challenge: Making an Early Diagnosis
  - Clinical and Imaging challenges
  - Imaging the Brain in AD, Approach

- Imaging Modalities
  - Structural /Radiologic
    - Ranking Modalities: Why is MRI better than CT
  - Functional/Nuclear Medicine
    - Ranking Modalities: Why is FDG PET-CT better than SPECT-CT

- The Bottom Line/Take Home
Functional nuclear medicine studies may detect findings suggestive of AD or other dementia before anatomic changes are revealed by radiologic studies.

May be used to confirm anatomic studies suspicion or subtle finding.
IMAGING MODALITIES

FUNCTIONAL

- Single Photon Emission Computed Tomography
  SPECT-CT

- Positron Emission Tomography
  PET-CT
IMAGING MODALITIES

FUNCTIONAL

• Single Photon Emission Computed Tomography

SPECT-CT

• Positron Emission Tomography

PET-CT
Hybrid SPECT–CT Scanner
Hybrid SPECT-CT
SPECT-CT

• The image is a map of cortical **perfusion**

• Uses a different tracer and different machine than PET
  – direct photon-emitting isotopes
  – average half-life of 6-12 hours, slightly more radiation than PET
  – Neurolite, Tc-99m bicisate dihydrochloride
  – Ceretec, Tc-99m exametazime
  – variety of tracers may be used for other nuclear studies: bone scan; whole body I-131 thyroid scan; parathyroid scans; myocardial perfusion; octreoscan
SPECT-CT in AD

AD look for:

- Preferential cortical lobar **hypoperfusion**
  - posterior temporal and parietal **sparing sensorimotor strip**
  - quite limited resolution for hippocampus
  - degree has been correlated with severity of dementia
  - specificity of SPECT *is contingent upon quantitative data.*

Puerto Rico issue:

- reported performance of SPECT revolves around semiquantitative computed assisted diagnostic software
- to our knowledge, only performed routinely on SPECT studies in PR @MEDFLIX

Dr. Carlos Jiménez Marchán, Nuclear Medicine Director
Display

Gray, black and white scale

Color scale – arbitrary colors, vendor specific

For today’s lecture:

Orange normal uptake
Purple decreased uptake
Green absent uptake
Coronal LT hipp  hyperfusion
SPECT axial – color scale
SPECT-CT axial, atrophy
### Scenium Analysis

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Side</th>
<th>Min SUV</th>
<th>Mean SUV</th>
<th>Max SUV</th>
<th>Mean # Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td>L</td>
<td>2.28</td>
<td>6.15</td>
<td>10.33</td>
<td>-1.3</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>R</td>
<td>2.40</td>
<td>6.77</td>
<td>10.89</td>
<td>-0.6</td>
</tr>
<tr>
<td>Central region</td>
<td>L</td>
<td>1.43</td>
<td>7.27</td>
<td>11.15</td>
<td>1.3</td>
</tr>
<tr>
<td>Central region</td>
<td>R</td>
<td>1.41</td>
<td>7.43</td>
<td>11.03</td>
<td>2.3</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>0.68</td>
<td>6.48</td>
<td>9.59</td>
<td>-0.8</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>0.70</td>
<td>6.56</td>
<td>10.29</td>
<td>1.9</td>
</tr>
<tr>
<td>Cingulate and paracingulate gyr</td>
<td>L</td>
<td>2.14</td>
<td>5.55</td>
<td>10.10</td>
<td>-3.1</td>
</tr>
<tr>
<td>Cingulate and paracingulate gyr</td>
<td>R</td>
<td>1.90</td>
<td>5.52</td>
<td>9.38</td>
<td>-2.5</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>L</td>
<td>0.74</td>
<td>6.59</td>
<td>11.43</td>
<td>-1.6</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>R</td>
<td>0.31</td>
<td>6.70</td>
<td>11.35</td>
<td>-1.2</td>
</tr>
<tr>
<td>Mesial temporal lobe</td>
<td>L</td>
<td>1.58</td>
<td>4.23</td>
<td>8.23</td>
<td>-5.8</td>
</tr>
<tr>
<td>Mesial temporal lobe</td>
<td>R</td>
<td>2.48</td>
<td>4.85</td>
<td>9.46</td>
<td>-2.8</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>L</td>
<td>1.20</td>
<td>7.35</td>
<td>11.31</td>
<td>-0.4</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>R</td>
<td>1.29</td>
<td>7.12</td>
<td>11.20</td>
<td>-0.7</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>L</td>
<td>1.05</td>
<td>7.39</td>
<td>12.34</td>
<td>0.2</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>R</td>
<td>0.67</td>
<td>6.83</td>
<td>10.04</td>
<td>-0.9</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>L</td>
<td>1.02</td>
<td>6.02</td>
<td>10.11</td>
<td>-3.6</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>R</td>
<td>1.40</td>
<td>6.17</td>
<td>10.36</td>
<td>-2.7</td>
</tr>
</tbody>
</table>
IMAGING MODALITIES

FUNCTIONAL

• Single Photon Emission Computed Tomography
  SPECT-CT

• Positron Emission Tomography
  PET-CT
Hybrid PET–CT Scanner
Hybrid PET-CT
PET-CT

With FDG, the image is a map of cortical and basal ganglionic glucose metabolism.

Uses different tracers and different machine than SPECT

- biologic compound labeled with a positron-emitting isotope, such as
  - carbon-11 (¹¹C)
  - oxygen-15 (¹⁵O)
  - fluorine-18 (¹⁸F)

- used because short half-lives (minutes to <2 hr.), allowing tracers to reach equilibrium in the body without prolonged radiation exposure

- **Glucose** is the main energy substrate of the brain.
- **F18 - FluoroDeoxyGlucose** is a glucose analogue.
FDG PET-CT in AD

AD look for:

**Preferential FDG cortical hypometabolism**

likely caused by a combination of

- neuronal cell loss and
- decreased synaptic activity

– mesial temporal/hippocampal
– parietal and posterior frontal sparing sensorimotor strip
– degree has been correlated with severity of dementia
– **PET** allows calculation of SUV (standardized uptake value) to which serial studies can be compared
FDG PET-CT in DDx of AD

Preferential FDG cortical hypometabolism

- FDG uptake patterns suggest specific types of dementia.
- Dementia of Parkinson disease pattern may be identical to AD pattern.
- Normal FDG pattern suggests a pseudodementia (depression) vs. false negative (too early).
FDG Uptake phase

• Scan started 60 min post injection to allow tracer distribution
• Patient rests in quiet place without visual or other sensory stimulation
Blood vessel

Brain Cortex

GLUT

K₁

K₂

Hexokinase

18FDG-1-P

18FDG-6P

18FDG

Glycogen

18FDG-6-phosphogluconolactone

HMP shunt

Glucose-6-phosphatase

18F-fru-6-P

Glycolysis

18FDG

GLUT-1

HIF1a (hypoxia)
Blood vessel

FDG-avid Cancer Cell

GLUT-1

HIF1a (hypoxia)

K1

K2

K3

K4

Glycogen

Hexokinase

Glucose-6-phosphatase

Glycolysis

18FDG-1-P

18FDG-6P

18FDG-6-phospho-gluconolactone

HMP shunt

18F-fru-6-P

Modified from Dr. Jaime Montilla
Normal Brain FDG PET-CT

• Uniform cortical metabolic uptake.
MIP = maximum intensity projection display

Normal uniform FDG cortical uptake
FDG PET-CT in AD

Puerto Rico issues

1. CAD software in FDG PET-CT
   - computed assisted diagnosis *increases diagnostic accuracy and specificity*
   - To our knowledge, performed routinely only PET studies in PR @ MEDFLIX
   - Dr. Carlos Jiménez Marchán, Nuclear Medicine Director

2. FDG
   - only commercially available PET tracer in PR
   - only currently CMS covered PET tracer
   - other brain and non brain tracers available
Quantitative Software

- Scenium (routinely used @ SP MEDFLIX for SPECT and PET).
  - Aids assessment by providing quantification
    - not a diagnostic software
  - Derived from FDG-PET scans of 30 ApoE4 neg. normal patients ranging in age from 54 to 72 years with normal neuropsychological tests
  - Software computes the number of SD from the mean for each voxel (volume element) compared to the normal brain
FDG PET-CT is not perfect for AD

Other functional etiologies for abnormal uptake
• Dementia of Parkinson disease presents identical uptake pattern as AD

Structural etiologies for abnormal uptake
• small vessel disease, vasculitis, infarcts
• tumor
• treated tumor, radionecrosis
## Scenium Analysis

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Side</th>
<th>Min SUV</th>
<th>Mean SUV</th>
<th>Max SUV</th>
<th>Mean # Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td>L</td>
<td>2.28</td>
<td>6.15</td>
<td>10.33</td>
<td>-1.3</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>R</td>
<td>2.40</td>
<td>6.77</td>
<td>10.89</td>
<td>-0.6</td>
</tr>
<tr>
<td>Central region</td>
<td>L</td>
<td>1.43</td>
<td>7.27</td>
<td>11.15</td>
<td>1.3</td>
</tr>
<tr>
<td>Central region</td>
<td>R</td>
<td>1.41</td>
<td>7.43</td>
<td>11.03</td>
<td>2.3</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>0.68</td>
<td>6.48</td>
<td>9.59</td>
<td>-0.8</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>0.70</td>
<td>6.56</td>
<td>10.29</td>
<td>1.9</td>
</tr>
<tr>
<td>Cingulate and paracingulate gyr</td>
<td>L</td>
<td>2.14</td>
<td>5.55</td>
<td>10.10</td>
<td>-3.1</td>
</tr>
<tr>
<td>Cingulate and paracingulate gyr</td>
<td>R</td>
<td>1.90</td>
<td>5.52</td>
<td>9.38</td>
<td>-2.5</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>L</td>
<td>0.74</td>
<td>6.59</td>
<td>11.43</td>
<td>-1.6</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>R</td>
<td>0.31</td>
<td>6.70</td>
<td>11.35</td>
<td>-1.2</td>
</tr>
<tr>
<td>Mesial temporal lobe</td>
<td>L</td>
<td>1.58</td>
<td>4.23</td>
<td>8.23</td>
<td>-5.8</td>
</tr>
<tr>
<td>Mesial temporal lobe</td>
<td>R</td>
<td>2.48</td>
<td>4.85</td>
<td>9.46</td>
<td>-2.8</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>L</td>
<td>1.20</td>
<td>7.35</td>
<td>11.31</td>
<td>-0.4</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>R</td>
<td>1.29</td>
<td>7.12</td>
<td>11.20</td>
<td>-0.7</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>L</td>
<td>1.05</td>
<td>7.39</td>
<td>12.34</td>
<td>0.2</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>R</td>
<td>0.67</td>
<td>6.83</td>
<td>10.04</td>
<td>-0.9</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>L</td>
<td>1.02</td>
<td>6.02</td>
<td>10.11</td>
<td>-3.6</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>R</td>
<td>1.40</td>
<td>6.17</td>
<td>10.36</td>
<td>-2.7</td>
</tr>
</tbody>
</table>
AGENDA

• The Challenge: Making an Early Diagnosis
  – Clinical and Imaging challenges
  – Imaging the Brain in AD, Approach

• Imaging Modalities
  – Structural /Radiologic
    • Ranking Modalities: Why is MRI better than CT
  – Functional/Nuclear Medicine
    • Ranking Modalities: Why is FDG PET-CT better than SPECT-CT

• The Bottom Line/Take Home
# PET vs. SPECT in Dementia


<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>79% (72-82)</td>
<td>82% (78-88)</td>
</tr>
<tr>
<td>PET</td>
<td>91% (86-94)</td>
<td>85% (79-91)</td>
</tr>
</tbody>
</table>
How good is PET-CT in differentiating between dementias?

• Multicenter study with 548 subjects of mild cognitive impairment (MCI)

• Correct classification:
  – 95% Alzheimer disease
  – 94% DLB
  – 92% FTD
  – 94% healthy

Why is FDG PET better than SPECT?

- Positrons are of higher energy than photons.
- PET crystals offer greater resolution increasing sensitivity, allowing more accurate localization of normal vs. pathologic tissue.
- Metabolism (PET) offers greater sensitivity than perfusion (SPECT).
SPECT vs. FDG PET
ORDER OF STUDIES’ SENSITIVITY FOR MAJOR DEMENTIA

PET-CT > SPECT-CT > MRI > CT
Requisition for FDG PET-CT scan

Do **not** write: *Rule out AD*

Must exclude secondary causes of dementia
- labs (vit. B 12, TFTs, metabolic panel, other)
- structural radiologic imaging (CT/MRI)

FDG PET-CT is used
when there is clinical difficulty differentiating between AD from other forms of neurodegenerative dementia.
Requisition for FDG brain PET-CT scan

Suggestion: create template

1. Write:
History: >6 month hx of worsening memory loss, starting_____.

2. Write: FDG brain PET-CT to guide diagnosis and treatment in differentiating AD vs. FTLD vs. other neurodegenerative process.

3. Specify if patient:
• Negative MRI/CT vs. MRI/CT suggestive of AD
• Negative laboratory workup (vit. B12, TFTs, metabolic panel)
• Include MMSE score or equivalent.
• Hypertensive and or diabetic?
• Documented microvascular ischemic disease or CADASIL?
• Parkinson disease?

4. Write (CMS): All information in patient’s record.
When to request nuclear medicine studies?

• Medicare age group:
  – follow CMS guidelines for reimbursement

• CT/MRI (structural imaging)
  – negative
  – equivocal or mildly positive

• Serial follow-up or clinical change in diagnosis.
When to request nuclear medicine studies?

Non-Medicare age group

• SPECT-CT usually covered by major commercial plans.
• PET-CT less likely to be covered by commercial plans.
• Worsening memory loss, unexpected for age when secondary causes have been excluded with labs and MRI
• Strong family history, patient symptomatic
• Strong family history, patient asymptomatic

Kindly include same workup results data in requisition as that for Medicare patients.

May help during preauthorization.
Case #1: AD vs. FTLD

- Negative metabolic workup, TFTs, and Vit. B12
- Negative brain MRI
- Negative SPECT for cortical hypoperfusion
FDG PET

Posterior frontal and anterior parietal cortical hypometabolism sparing sensorimotor strip; mesial temporal hypometabolism.
Alzheimer disease
DDx: PD dementia
Quantitative Assessment routinely performed @ MEDFLIX.
Alzheimer’s Disease

- First described in 1906 by Alois Alzheimer
- Most common neurodegenerative dementia,
  - 2/3 of all cases.
  - More common in women.
- Predilection for mesial temporal, posterior aspect of parietal lobes and posterior aspect of frontal lobes.
- Spares precentral (motor) and postcentral (sensory) gyri.
- Usually starts mesial temporal, then progresses to parietal and frontal.
- CT, MRI and SPECT may be normal
- PET abnormal before other studies
- FDG PET does not measure amyloid β plaques
Microscope image showing beta-amyloid (brown) brain plaques in Alzheimer's disease. — Wiki Commons
Case #2: AD vs. FTLD

- Negative brain MRI
- Negative metabolic workup, TFTs and Vit. B12
Predilection for anterior frontal and anterior temporal lobes cortical hypometabolism.
FTLD
<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Side</th>
<th>Min SUV</th>
<th>Mean SUV</th>
<th>Max SUV</th>
<th>Mean # Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central region</td>
<td>L</td>
<td>0.32</td>
<td>5.03</td>
<td>7.82</td>
<td>0.7</td>
</tr>
<tr>
<td>Central region</td>
<td>R</td>
<td>0.39</td>
<td>4.82</td>
<td>8.02</td>
<td>0.0</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>1.35</td>
<td>4.68</td>
<td>6.67</td>
<td>0.3</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>0.67</td>
<td>4.54</td>
<td>6.80</td>
<td>0.7</td>
</tr>
<tr>
<td>Cingulate and paracingulate gyri</td>
<td>L</td>
<td>1.21</td>
<td>4.73</td>
<td>7.56</td>
<td>-0.3</td>
</tr>
<tr>
<td>Cingulate and paracingulate gyri</td>
<td>R</td>
<td>1.21</td>
<td>4.38</td>
<td>7.60</td>
<td>-0.9</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>L</td>
<td>0.37</td>
<td>4.86</td>
<td>7.71</td>
<td>-0.7</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>R</td>
<td>0.93</td>
<td>4.87</td>
<td>8.29</td>
<td>-0.6</td>
</tr>
<tr>
<td>Mesial temporal lobe</td>
<td>L</td>
<td>1.67</td>
<td>3.95</td>
<td>5.60</td>
<td>0.1</td>
</tr>
<tr>
<td>Mesial temporal lobe</td>
<td>R</td>
<td>2.37</td>
<td>4.07</td>
<td>5.58</td>
<td>0.3</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>L</td>
<td>1.16</td>
<td>5.27</td>
<td>8.20</td>
<td>-0.1</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>R</td>
<td>1.28</td>
<td>5.10</td>
<td>7.79</td>
<td>-0.5</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>L</td>
<td>0.72</td>
<td>5.04</td>
<td>7.69</td>
<td>-0.6</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>R</td>
<td>0.41</td>
<td>4.84</td>
<td>7.71</td>
<td>-0.9</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>L</td>
<td>1.30</td>
<td>4.82</td>
<td>7.39</td>
<td>-1.1</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>R</td>
<td>1.18</td>
<td>4.62</td>
<td>7.16</td>
<td>-1.7</td>
</tr>
</tbody>
</table>
FTLD (previously Pick’s Disease)

- Frontotemporal lobe degeneration
- Cognitive and language dysfunction and behavioral changes.

Spherical argyrophilic (silver staining) tau protein fibrils, disorderly array
Case #3: AD vs. FTLD vs. LBD

- Negative brain MRI
- Rapidly progressive fluctuating cognitive decline.
  - Visual hallucinations.
Parietal and mesial temporal cortical hypometabolism (similar to AD) but also with occipital involvement.
<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Side</th>
<th>Min SUV</th>
<th>Mean SUV</th>
<th>Max SUV</th>
<th>Mean # Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td>L</td>
<td>1.41</td>
<td>6.54</td>
<td>13.40</td>
<td>0.4</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>R</td>
<td>1.66</td>
<td>7.03</td>
<td>12.71</td>
<td>0.8</td>
</tr>
<tr>
<td>Central region</td>
<td>L</td>
<td>0.47</td>
<td>7.18</td>
<td>11.76</td>
<td>2.3</td>
</tr>
<tr>
<td>Central region</td>
<td>R</td>
<td>0.75</td>
<td>7.12</td>
<td>11.43</td>
<td>2.6</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>1.14</td>
<td>6.21</td>
<td>9.63</td>
<td>-0.1</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>0.78</td>
<td>6.16</td>
<td>9.73</td>
<td>1.3</td>
</tr>
<tr>
<td>Cingulate and paracingulate gyri</td>
<td>L</td>
<td>1.59</td>
<td>6.57</td>
<td>11.18</td>
<td>0.4</td>
</tr>
<tr>
<td>Cingulate and paracingulate gyri</td>
<td>R</td>
<td>1.71</td>
<td>6.42</td>
<td>11.18</td>
<td>0.6</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>L</td>
<td>0.97</td>
<td>7.33</td>
<td>11.63</td>
<td>2.5</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>R</td>
<td>1.03</td>
<td>7.38</td>
<td>11.71</td>
<td>2.8</td>
</tr>
<tr>
<td>Mesial temporal lobe</td>
<td>L</td>
<td>1.93</td>
<td>5.75</td>
<td>8.61</td>
<td>2.3</td>
</tr>
<tr>
<td>Mesial temporal lobe</td>
<td>R</td>
<td>2.41</td>
<td>6.04</td>
<td>8.83</td>
<td>2.4</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>L</td>
<td>0.79</td>
<td>6.45</td>
<td>10.08</td>
<td>-2.0</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>R</td>
<td>1.27</td>
<td>6.51</td>
<td>9.87</td>
<td>-1.5</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>L</td>
<td>0.45</td>
<td>6.16</td>
<td>10.64</td>
<td>-2.4</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>R</td>
<td>0.45</td>
<td>6.00</td>
<td>10.60</td>
<td>-2.5</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>L</td>
<td>1.72</td>
<td>6.39</td>
<td>10.20</td>
<td>-1.3</td>
</tr>
</tbody>
</table>
Lewy Bodies Dementia (LBD)

- Metabolic pattern of AD + occipital lobes
- Progresses often faster than AD.
- Fluctuating symptoms may seem patient is faking the condition (over hours or days).
- Definitive diagnosis post-mortem.
Histopathology: Lewy Bodies

Circular eosinophilic neuronal inclusions with central protein core. Peripheral halo from accumulation of damaged cytoskeletal elements.
Case #4: AD vs. FTLD vs. other

- Negative labs.
- Brain MRI negative for preferential atrophy.
Normal study

• Consider pseudodementia in the proper clinical setting produced by depression or other affective disorder.
ORDER OF STUDIES’ SENSITIVITY FOR MAJOR DEMENTIA

PET-CT > SPECT-CT > MRI > CT
AD – Histopathology at autopsy

- Tangled bundle of fibrils within neurons, intraneuronal neurofibrillary tangles (NFT)
- Globs of sticky proteins, β-amyloid [Aβ] plaques) in the extracellular spaces between neurons
Pending CMS approval – NOT available in PR

Imaging pathology in the living patient

- β amyloid neuritic plaque specific and tau protein PET radiotracers:
  - Florbetapir F18 (AMYViD), FDA approved 4/2012
  - Flutemetamol F18 (Vizamyl), FDA approved 10/2013
    Pittsburgh compound B (PIB) derivative
  - Floretaben F18 (Neuraceq), FDA approved 3/2014
  - IDEAS - Imaging Dementia Evidence Amyloid Scanning
    - Data demonstrating change in diagnosis and management

- Tau protein PET radiotracer.
  - F18 AV1451 pathologic aggregation of tau protein
    - associated with anatomic patterns of neurodegeneration and clinical manifestations of AD
β-Amyloid PET vs. Autopsy Immunohistochemistry

Normal scan

Mild to moderate

Severe

Use of Florbetapir-PET for Imaging β-Amyloid Pathology
Clark, et al. JAMA. 2011;305(3):275-283
ORDER OF STUDIES’ SENSITIVITY FOR MAJOR DEMENTIA

β-A or tau protein specific PET-CT

FDG PET-CT > SPECT-CT > MRI > CT
AGENDA

• The Challenge: Making an Early Diagnosis
  – Clinical and Imaging challenges
  – Imaging the Brain in AD, Approach

• Imaging Modalities
  – Structural /Radiologic
    • Ranking Modalities: Why is MRI better than CT
  – Functional/Nuclear Medicine
    • Ranking Modalities: Why is FDG PET-CT better than SPECT-CT

• The Bottom Line/Take Home
Take Home

• MRI is the preferred initial imaging study for evaluation of neurodegenerative dementia.

• Requires dedicated hippocampal views.
Take Home

• **FDG PET-CT is the most sensitive and specific imaging study** for Alzheimer disease covered by CMS.

• **Should be requested following CMS requirements in Medicare population.**
Take Home

• SPECT-CT and FDG PET-CT should be routinely performed using semiquantitative analysis.

• Functional nuclear medicine studies may detect findings suggestive of AD and other neurodegenerative disorders before anatomic changes are unveiled by structural radiologic studies.
In the setting of Alzheimer disease.

___ MRI and SPECT-CT are more sensitive than FDG PET-CT.

___ The correct way to request a PET-CT is: “rule out Alzheimer disease.”

___ It is crucial to review all prior cerebral anatomic studies, including CT and MRI scans of the brain, and prior nuclear medicine brain SPECT-CT during the interpretation of FDG PET-CT.

___ Functional nuclear medicine studies may detect findings suggestive of AD before anatomic changes are revealed by radiologic (CT/MRI) studies.
In the setting of Alzheimer disease.

**False:** MRI and SPECT-CT are more sensitive than FDG PET-CT.

___ The correct way to request a PET-CT is: “rule out Alzheimer disease.”

___ It is crucial to review all prior cerebral anatomic studies, including CT and MRI scans of the brain, and prior nuclear medicine brain SPECT-CT during the interpretation of FDG PET-CT.

___ Functional nuclear medicine studies may detect findings suggestive of AD before anatomic changes are revealed by radiologic (CT/MRI) studies.
In the setting of Alzheimer disease.

**False:** MRI and SPECT-CT are more sensitive than FDG PET-CT.

**False:** The correct way to request a PET-CT is: “rule out Alzheimer disease.”

- It is crucial to review all prior cerebral anatomic studies, including CT and MRI scans of the brain, and prior nuclear medicine brain SPECT-CT during the interpretation of FDG PET-CT.

- Functional nuclear medicine studies may detect findings suggestive of AD before anatomic changes are revealed by radiologic (CT/MRI) studies.
Question  True or False

In the setting of Alzheimer disease.

False: MRI and SPECT-CT are more sensitive than FDG PET-CT.

False: The correct way to request a PET-CT is: “rule out Alzheimer disease.”

True: It is crucial to review all prior cerebral anatomic studies, including CT and MRI scans of the brain, and prior nuclear medicine brain SPECT-CT during the interpretation of FDG PET-CT.

___ Functional nuclear medicine studies may detect findings suggestive of AD before anatomic changes are revealed by radiologic (CT/MRI) studies.
In the setting of Alzheimer disease.

**False:** MRI and SPECT-CT are more sensitive than FDG PET-CT.

**False:** The correct way to request a PET-CT is: “rule out Alzheimer disease.”

**True:** It is crucial to review all prior cerebral anatomic studies, including CT and MRI scans of the brain, and prior nuclear medicine brain SPECT-CT during the interpretation of FDG PET-CT.

**True:** Functional nuclear medicine studies may detect findings suggestive of AD before anatomic changes are revealed by radiologic (CT/MRI) studies.
Gracias por su atención

fzalduondo@spmedflix.com
MRI – beyond atrophy

• Functional MRI (fMRI)
  – DSC – dynamic susceptibility contrast
    • measures cerebral perfusion with IV gadolinium
    • correlates with SPECT and PET studies
  – Activational – BOLD - blood oxygenation level– dependent
  – Not routinely performed on OPD or IP setting
  – Software and processing power may not be available
  – Not all neuro/radiologists cognizant
  – Not covered by insurance or CMS
PET-MRI will replace PET-CT

- No ionizing radiation inherent to CT
- Superior soft tissue contrast compared to CT
- Neuropsychiatric PET - superior in correlating PET with hippocampal atrophy
- Neurooncologic PET – superior resolution for brain tumors
- Oncologic PET – greater resolution and sensitivity for solid organ lesions
- Not available in Puerto Rico
PET-MRI  FDA approved 2011
DaTscan (I–123)
Striatal Dopamine Transporter

Normal uptake in symptomatic patient
Essential tremors
Drug induced parkinsonism
DaTscan (I–123) Striatal Dopamine Transporter

Abnormal Parkinsonian syndromes
- Progressive supranuclear palsy
- Multiple system atrophy
- Idiopathic Parkinson’s disease

Lewy Bodies