Alzheimer’s Imaging

Homayoun Modarresifar, M.D.
Clinical Assistant professor
Department of Psychiatry
East Tennessee State University

Introduction

Why Alzheimer’s Disease (AD) is important?
AD is a progressive, fatal brain disease. AD is the most common form of dementia among older people (60% of dementia subtypes)
Increasing age is the primary risk factor for developing AD; although severe memory loss is not a normal part of aging
Alzheimer’s Association report in 2011 shows 5.4 million people in the U.S. have AD
Without successful treatment, there will be 16 million Americans and 106 million people worldwide with AD by 2050

Introduction...

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Pathology and Etiology

- Initial damage of neurons in temporal lobes and later in neocortex
- Extracellular beta amyloid plaques and intracellular neurofibrillary tangles (tau protein)
- Plaque build up induces inflammation causing injury in hippocampus and cerebral cortex

Brain Imaging Approaches

- **Structural MRI**
  - New measures and New analysis techniques

- **Functional MRI**
  - Early changes in function

- **Brain SPECT**
  - Tc-99m HMPAO

- **Positron Emission Tomography**
  - 18F-Fluorodeoxyglucose (FDG)
  - New radioisotopes; 11-C, 15-O and other 18-F radioligands

MRI in Alzheimer’s Disease

- Comfort claustrophobia
  - Acquisition: better scanners
  - Analysis: better ways of looking at the data
  - Dynamic measures (versus static); Functional MRI
  - New types of measurements (location, thickness versus size)
Manual Measurement of the structures on MRI

Functional MRI

Brain uptake of Tc-99m based lipid-soluble radionuclide
- 89% sensitivity and 80% specificity for AD
- Bilateral posterior perfusion abnormality associated with AD
- Frontal perfusion deficit associated with front temporal dementia
- Patchy uptake pattern associated with vascular dementia

SPECT imaging

Normal  TBI - Traumatic Brain Injury  Alzheimer's Disease
PET Scanner

PET imaging

- FDG uptake and blood flow
- Deficits in temporo-parietal metabolism are seen in patients with AD
- Sparing of basal ganglia, thalamus, cerebellum, and primary sensori-motor complex
- Sensitivity 87-96%, 73% specificity

New Isotopes
- Direct measures of Amyloid
- Measures of neurotransmitters

PET Imaging...

Normal brain

- In the brain glucose is preferentially used as a source of energy.
- Gray matter is particularly FDG-avid with uptake levels similar to that seen in malignancy.
Agents used in PET imaging are produced in a cyclotron by bombarding a stable element with protons, deuterons, or helium nuclei.

The resulting isotope will contain excess protons and will decay by positron emission.

PET imaging utilizes physiologic substrates labeled with these positron emitting isotopes.

**Physical principles of PET**

PET uses radioactive materials to track specific aspects of brain function

Add a radioisotope to a substrate for brain: glucose (18FDG); water (H2O 15)

Neurotransmitter or precursor (dopamine, serotonin, etc)

Attach to Amyloid plaques

**Positron Emitters**

- 18F-FDG is a glucose analog with replacement of the oxygen in C-2 position with 18-fluorine.
- FDG cannot enter glycolysis, therefore it becomes trapped intra-cellularly as FDG-6-Phosphate.

**18-F FDG**

- Imaging technique that provides information on brain structure and biochemical basis of brain function
- Studies of glucose metabolism using 18-F-fluorodeoxyglucose (FDG) demonstrate metabolic patterns reflecting neuronal function specific to different dementias

**Positron Emission Tomography (PET)**
Fusion PET-CT images are more effective than PET images alone in distinguishing normal uptake from neoplastic lesions.

PET-CT can lead to a significant change in impression, diagnostic accuracy, and fewer equivocal lesions.

PET/CT is useful in early diagnosis of dementia subtypes.

American Academy of Neurology Practice Parameter Guidelines recommend structural imaging in initial evaluation of dementia.

Positron Emission Tomography (PET) with FDG helps differentiate (AD) from Front temporal Dementia (FTD).

Other PET technologies/positron emitters are under development.

PET/CT is useful in early diagnosis of dementia subtypes.

Normal Alzheimer’s
Alzheimer’s
Pick’s
Multiple Infarct Dementia

Glucose Metabolic Patterns in Dementia

PET Cerebral Metabolism in Alzheimer’s Disease Progression and in Normal Brains
PET AND GENETIC RISK FOR AD

No APOE-4    APOE-4

Genetic Risk:

Lower inferior parietal metabolism in non-demented persons with a single copy of APOE-4

PET Imaging

NORMAL MEMORY    DEMENTIA

-18%    -12%    -20%    -22%

PIB and FDG Distribution

- Fluorescent small molecule probe
- Neutral, lipophilic probe originally developed for use with fluorescence microscopy
- Fluorinated analogue (FDDNP) provides visualizations of NFTs and diffuse amyloid

Other tracers

Pittsburgh Compound B
An elderly patient with memory problems has decreased MMSE compared to the last year evaluation (now is borderline normal).

Her MRI shows mild brain atrophy.

What is the next step?

- Repeat MMSE is 6 months
- Repeat structural MRI in 6 months
- Order brain CT with contrast
- Order brain SPECT Imaging (HMPAO or ECD)
- Order brain PET/CT Imaging (FDG or Florpiramin)

Choose 2 answers
Case 1 (Oops! I forgot!)

- Potential to detect the preclinical stage
- Treatments will more likely slow or halt, rather than reverse, the disease
- Identify an earlier time to intervene
- Help determine when to intervene
- Useful as a marker of change/intervention effects
- Imaging outcome measures vs. disease outcome

Why is imaging important?

- Neurodegenerative dementia present on autopsy?
  - Yes 113 4
  - No 7 14
  - Accuracy of FDG-PET for Assessing Neurodegenerative Dementia
  - Sensitivity = 94%
  - Specificity = 78%
  - Accuracy = 92%

- Alzheimer’s disease found on autopsy?
  - Yes 91 11
  - No 6 30
  - Accuracy of FDG-PET for Assessing Alzheimer’s Disease
  - Sensitivity = 94%
  - Specificity = 73%
  - Accuracy = 88%
Progressive dementia actually present?

<table>
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Accuracy of FDG-PET for Assessing Progressive Dementia

- AD and other progressive dementias significantly alter brain metabolism early, relative to the manifestations of cognitive symptoms.
- Clinical FDG-PET detects this altered metabolism, providing an accurate clinical tool for noninvasive prognostic and diagnostic assessment.

Brain Areas with Lowered Glucose Metabolism in Alzheimer’s Disease

Brain Areas with Significant 1-Year Decline in Glucose Metabolism in Alzheimer’s Disease
PET neurochemical phenotyping for mild, early dementia produces significantly different results than the best clinical expert phenotyping.

Amyloid and presynaptic dopamine imaging can identify subtypes of dementia.

PET scans provide images of important signals for disease that other examinations missed, such as deposits of amyloid plaque; a common indicator of Alzheimer’s disease and damage to dopamine nerves in Lewy body dementia.

**PET Scans Improve Accuracy of Diagnosis in Early Onset Disease**

<table>
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<tr>
<th>PET Imaging Diagnosis</th>
<th>AD</th>
<th>DLB</th>
<th>FTD</th>
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<tr>
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Clinical Consensus vs. PET Diagnosis

- Front temporal dementias: decreased uptake in frontal and anterior temporal regions
- Depression: decreased anterior brain metabolism; more pronounced on the left.
- Vascular: patchy defects in central white matter
- Lewy body: deficits in occipital lobes and cerebellum

**PET in Dementia**

- Pattern of decreased FDG in AD in parietotemporal cortex; sparing basal ganglia, thalamus, cerebellum, brainstem and cortical regions mediating sensory and motor functions.
- Extent of hypo metabolism correlates with severity of cognitive impairment.
- May be unilateral early, more symmetric as disease progresses
Alzheimer’s Disease

“Vascular” dementia preferred over “multi-infarct” dementia, because the former acknowledges the many vascular causes that can contribute to dementia.

About 15% of all dementias

Infarcts that take progressive “bites out of the pie” with continued loss of brain tissue

Vascular dementia is characterized by a stepwise course with periods of stability followed by sudden decline in cognitive function.

Multi-infarct (vascular) dementia

CT of lacunar infarcts
“Etat lacunaire”: clinical syndrome in hypertensive and/or diabetic patients with primarily motor deficits

- Subcorticoarteriosclerotic encephalopathy (Binswanger’s disease): white matter demyelinization and gliosis instead of discrete infarcts
- 90% hx of high BP and strokes, lacunes seen

Multi-infarct (vascular) dementia

MRI of Deep White Matter Infarcts

- MRI and CT are the best ways to evaluate
- Perfusion images show patchy asymmetric, bilateral areas of decreased perfusion in the basal ganglia, central white matter and cortical regions

Multi-infarct (vascular) dementia
First symptoms are often personality change:
- Apathy and indifference toward customary interests
- Disregard for social decorum
- Poor social judgment, inappropriate sexual advances, coarse and jocular demeanor
- Not necessarily highly forgetful

Pick’s Disease – Hx, Sx

Can't initiate, organize, and follow through on even very simple plans
- Normal visual/spatial function (intact parietal function)
- Begins after age 40 and is less common after age 60
- Progressive
- Rare, 5-10% of dementias

Pick’s Disease – Hx, Sx ...

Primarily frontal and anterior temporal lobe atrophy
- Spares the parietal areas
- “Pick bodies” found in affected brain cells
- Neurons swell and appear ballooned

Pick’s Disease – Distribution, Pathology
- Fluctuating confusion, attention, and alertness
- Disturbance of consciousness
- Visual hallucinations
- Delusions
- Memory impairment
- Parkinsonian movements

**Dementia with Lewy bodies - Sx**

- Hallmark is the Lewy body
- Primary constituent is alpha-synuclein
- Presynaptic protein
- Unknown function
- Neurofilament proteins and ubiquitin

**Dementia with Lewy bodies - Pathology**

Thank you for your attendance