Alzheimer Disease

TERMINOLOGY
- Alzheimer disease (AD)
  - Progressive neurodegenerative disease of brain of unknown etiology generally characterized by impairments in episodic memory and other cognitive domains
  - Likely related to amyloid-beta (Aβ) and tau aggregation leading to synaptic dysfunction, neuronal/glial cell death

IMAGING
- Amyloid PET
  - Increased brain amyloid gray matter on PET is early biomarker in AD and appears prior to clinical symptoms
  - Absence of amyloid plaque rules out AD in patients with dementia
  - Positive scans do not in themselves diagnose AD and must be correlated with clinical symptoms
  - 10-20% of cognitively normal adult population has positive scans of uncertain significance

  - Decreased gray-white matter differentiation in at least 2 regions or single area of focally increased gray matter uptake are signs of positive florbetapir study
  - Changes generally seen prior to F-18 FDG PET/MR abnormalities
- F-18 FDG PET
  - Glucose hypometabolism in parietotemporal and posterior cingulate cortices; usually bilaterally symmetrical
  - Glucose hypometabolism continues to worsen with disease progression
- SPECT
  - 2nd-line study if PET is not available/reimbursed
- MR
  - Atrophy of medial temporal lobe structures (entorhinal cortex, hippocampus), visible as early as MCI

CLINICAL ISSUES
- Most common cause of dementia (60-80% of cases)

(Left) Axial F-18 florbetapir PET in a patient with mild cognitive impairment (MCI) demonstrates homogeneous uptake throughout the brain, without clear distinction between gray and white matter, consistent with heavy β-amyloid deposition in gray matter, which is seen in Alzheimer disease (AD). (Right) Axial F-18 florbetapir PET demonstrates characteristic physiologic uptake in the white matter but no significant uptake in the gray matter. This clear distinction indicates no detectable amyloid deposition.

(Left) Sagittal F-18 florbetapir PET shows normal gray-white differentiation in the precuneus, a region often affected in AD. (Right) Sagittal F-18 florbetapir PET shows diffuse activity without gray-white differentiation in the precuneus, consistent with β-amyloid deposition.
### Alzheimer Disease

**TERMINOLOGY**

**Definitions**

- **Alzheimer disease (AD)**
  - Progressive neurodegenerative brain disease generally characterized by impairments in episodic memory and other cognitive domains
  - Likely related to amyloid-beta (Aβ) and tau aggregation leading to synaptic dysfunction, neuronal/glial cell death
  - Role of imaging
    - Early detection of preclinical AD
    - Diagnosis of AD with clinical presentation and other biomarkers
    - Differential diagnosis between AD and other causes of dementia

**IMAGING**

**General Features**

- **Best diagnostic clue**
  - **Preclinical AD**
    - Amyloid PET positive
    - Mild characteristic F-18 FDG PET hypometabolism in select areas
    - Early MR changes
  - **Early AD**
    - Amyloid PET positive
    - F-18 FDG PET and MR abnormalities become more evident
  - **Late AD**
    - Amyloid and F-18 FDG PET grossly positive
    - More extensive atrophy present (CT/MR)

**Nuclear Medicine Findings**

- **Amyloid PET**
  - F-18 florbetapir, flutemetamol, and florbetaben tracers are FDA approved
  - Increased brain amyloid in gray matter on PET
    - Early biomarker in AD, prior to clinical symptoms
    - Changes generally seen prior to F-18 FDG PET/MR abnormalities
  - Absence of amyloid plaque rules out AD in patients with dementia
  - Positive scans do not in themselves diagnose AD and must be correlated with clinical symptoms
  - 10-20% of cognitively normal adult population has positive scans (uncertain significance)
  - Interpretation of amyloid PET images
    - View in black-on-white background at high contrast levels
      - Axial images 1st
      - Coronal and sagittal views for confirmation of findings
    - Cerebellum gray-white differentiation is baseline for discerning normal gray matter from physiologic tracer retained in white matter
    - Signs of amyloid deposition
      - Decreasing cortical gray-white differentiation compared to cerebellar gray-white differentiation
      - Increasing gray matter uptake in temporal, parietal, and frontal cortices
  - Uptake in posterior cingulate gyrus and precuneus (may be early deposition sign)
  - F-18 florbetapir: Decreased gray-white matter differentiation in at least 2 regions or single area of focally increased gray matter uptake = positive
  - Occipital gray matter is less often amyloid positive
  - Artifacts and pitfalls
    - Severely diminished gray matter volume in AD patients may make abnormal exam appear normal due to contoured cortex
    - Fused PET/CT images as supplement to evaluate uptake relative to white and gray matter
    - Highest transaxial images above orbits often have diminished gray-white matter differentiation, even in normal patients

- **F-18 FDG PET**
  - General F-18 FDG uptake patterns
    - **Mild cognitive impairment (MCI)**
      - Medial temporal lobe hypometabolism: Most sensitive marker for predicting MCI
    - **Early AD**
      - Relative reduction in activity in parietal, temporal lobes and posterior cingulate gyri
      - Usually symmetric
      - Posterior cingulate cortex hypometabolism: Most sensitive marker for predicting MCI → AD
    - **Early and advanced AD**
      - Sparing of sensory motor cortex, basal ganglia, thalamus, primary visual cortex
    - **Advanced AD**
      - Progression of findings present in early AD
      - Usually symmetric
      - Frontal lobe hypometabolism
      - Moderate to severe atrophy
  - F-18 FDG PET most accurate when read in conjunction with quantitation software that compares F-18 FDG uptake in patient against uptake from normal database
  - SPECT with Tc-99m HMPAO or Tc-99m ethyl cysteinate dimer (ECD) has similar appearance as PET but ↓ resolution and sensitivity

**MR Findings**

- **T1WI, T2WI**
  - Atrophy of medial temporal lobe structures (entorhinal cortex, hippocampus) visible as early as MCI
  - Rates of whole-brain and hippocampal atrophy may be used to monitor progression of neurodegeneration
  - Often with coexisting microvascular disease and white matter hyperintensities

**Imaging Recommendations**

- **Best imaging tool**
  - Amyloid PET best for ruling out AD
  - Amyloid and F-18 FDG PET can help to differentiate between AD and other causes of dementia (frontotemporal dementia, Lewy body dementia)
  - PET may be used in early diagnosis of preclinical AD
  - Correlate imaging results with clinical picture and other biomarkers of AD

- **Protocol advice**
  - Amyloid PET
Central Nervous System

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– Patient preparation
  □ Patient needs to lie still for 20-30 min, so immobilization techniques may be necessary
– Radiopharmaceutical
  □ F-18 flurbetapir (Amyvid)
  □ F-18 flutemetamol (Vizamyl)
  □ F-18 flurbetaben (Neuraceq)
– Dose: 10 mCi (370 MBq)
– Dosimetry: Gallbladder wall receives highest dose, followed by intestines
– Image acquisition
  □ Depends largely on available PET scanner
  □ CT typically used for attenuation correction; older PET scanners may use separate source (such as Ge-68/68-Ga) for transmission scan
  □ Imaging begins 30-60 min after injection
  □ 20-30 min static images typically done in clinical setting
  □ Matrix: Transaxial 128 x 128 or 256 x 256
  □ Pixel size: 2-4 mm
  □ Filtered back projection or iterative reconstruction

F-18 FDG PET
– Patient preparation
  □ Patient should fast, stop IV fluids containing dextrose, stop parenteral feeding for 4-6 h
  □ Blood sugar should be < 150-200 mg/dL
  □ Patient should be placed in quiet, dimly lit room prior to and after injection for 30 min
– Radiopharmaceutical: F-18 FDG
– Dose: 5-20 mCi (185-740 MBq)
– Dosimetry: Urinary bladder receives largest dose
– Image acquisition: 30-60 min after injection

SPECT
– 2nd-line study if PET is not available/reimbursed
– Patient preparation
  □ Place patient in quiet, dimly lit room prior to and after injection for 30 min
– Radiopharmaceutical
  □ Tc-99m exametazime (HMPAO)
  □ Tc-99m bicisate (ECD)
– Dose: 15-30 mCi (555 MBq to 1.1 GBq)
– Dosimetry
  □ Tc-99m HMPAO: Kidneys receive highest dose
  □ Tc-99m ECD: Bladder wall receives highest dose
– Image acquisition
  □ Optimal imaging time for Tc-99m HMPAO: 90 min post injection
  □ Optimal imaging time for Tc-99m ECD: 45 min post injection

DIFFERENTIAL DIAGNOSIS

Vascular Dementia (Multiinfarct Dementia)
● Impaired blood supply to brain regions
● 2nd most common cause of dementia
● Global atrophy with diffuse white matter lesions/infarcts that generally correlate with cognitive symptoms

Alzheimer Disease Mixed Dementia
● AD and vascular dementia

Lewy Body Disease
● Commonly presents with hallucinations, sleep disturbances, and parkinsonian motor features
● F-18 FDG PET hypometabolism in occipital cortex distinguishes from AD

Frontotemporal Dementia
● Commonly presents with personality and behavioral changes
● Atrophy of frontal and anterior temporal lobes
● F-18 FDG PET hypometabolism primarily in frontal and anterior temporal lobes distinguishes from AD mixed dementia
● Composed of characteristic features of > 1 type of dementia; commonly includes AD

Creutzfeldt-Jakob Disease
● Rapidly fatal, prion-related disease with impairments in cognition and behavioral changes
● DWI MR: Hyperintensity in striatum, cingulum, neocortex

Progressive Supranuclear Palsy
● Signs and symptoms of dementia plus gait, balance, and eye movement abnormalities

Corticobasal Degeneration
● Progressive disorder of nerve cell loss/atrophy (cerebral cortex and basal ganglia)
● Cognitive dysfunction and movement disorders

Causes of Reversible Dementia
● Normal pressure hydrocephalus
● Hypothyroidism
● Infections: Neurosyphilis, HIV
● Trauma (e.g., chronic subdural hematoma)
● Tumor, other mass lesions
● Depression
● Vitamin B12 deficiency

Other Neurodegenerative Disease
● Parkinson disease
● Huntington disease

PATHOLOGY

General Features
● Etiology
  ○ Most likely combination of genetic, lifestyle, and environmental factors
  ○ Probable role of Aβ and tau in pathogenesis
  ○ Accumulation of extracellular amyloid plaques contributes to disrupted synaptic communication and neuronal death
  ○ Accumulation of intracellular tau tangles contributes to disruption of nutrient and molecular transfer and neuronal death
● Genetics
  ○ Early-onset, familial AD
    – Single-gene mutation
      □ Amyloid precursor protein (APP) gene on chromosome 21
      □ Presenilin 1 (PSEN1) gene on chromosome 14
      □ Presenilin 2 (PSEN2) gene on chromosome 1

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- Results in formation of abnormal proteins involved in APP
  - May contribute to production of harmful forms of Aβ and Aβ-related pathology
- Late-onset, sporadic AD
  - Significant risk is related to APOE gene on chromosome 19
  - APOE plays role in cholesterol transport and Aβ maintenance
  - APOE exists as 3 alleles (e2, e3, e4) with each individual carrying 2 copies
  - ApoE-e4 allele is present in 20-30% of USA population and confers increased risk for AD development
  - 40-65% of individuals with AD carry at least 1 copy of e4 allele

CLINICAL ISSUES

Presentation
- Most common signs/symptoms
  - Significant impairment in memory and cognition
  - Mood and personality changes
- Clinical profile
  - Preclinical AD
    - Amyloid PET turns positive during this period
    - No noticeable symptoms of AD with early AD brain changes (up to 20 years before symptoms)
  - MCI due to AD
    - Change in cognition within 1 or more cognitive domains with functional independence intact
  - Possible AD
    - Significant cognitive/behavioral symptoms
      - Must represent change from prior status
      - Must interfere with functional ability
      - In presence of sudden onset &/or another disorder that could cause similar symptoms, such as cerebrovascular disease
  - Probable AD
    - Insidious change of cognitive/behavioral symptoms that interferes with functional ability
    - Not in presence of another disorder that could cause similar symptoms
  - Visual variant of AD
    - Impaired visuospatial skills without memory complaints

Demographics
- Epidemiology
  - Estimated 5.2 million Americans affected by AD
  - Most common cause of dementia (60-80% of cases)
  - Prevalence
    - ~ 11% of adults ≥ 65 years
    - ~ 32% of adults ≥ 85 years

Treatment
- No current disease-modifying treatment for AD
- Cholinesterase inhibitors may delay worsening of cognitive symptoms for 6-12 months
- NMDA inhibitors may temporarily delay worsening of symptoms

DIAGNOSTIC CHECKLIST

Key Imaging Findings
- Preclinical AD
  - Amyloid PET positive
  - F-18 FDG PET hypometabolism
  - Early MR changes
- Early AD
  - PET/MR abnormalities become more evident
- Late AD
  - F-18 FDG and amyloid PET grossly positive
  - More extensive atrophy present on CT/MR

SELECTED REFERENCES
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(Left) Axial F-18 florbetapir PET in a patient with MCI demonstrates homogeneous uptake throughout the brain, without clear distinction between gray and white matter, consistent with heavy β-amyloid deposition in gray matter, which is seen in AD. (Right) Axial F-18 florbetapir PET shows uptake in the white matter but no significant uptake in the gray matter throughout, especially in the precuneus, indicating no detectable amyloid deposition.

(Left) More inferior axial F-18 florbetapir PET in the same patient shows homogeneous uptake throughout the brain, without clear distinction between gray and white matter in the temporal lobe, consistent with heavy β-amyloid deposition in gray matter, which is seen in AD. (Right) More inferior axial F-18 florbetapir PET in the same patient demonstrates characteristic uptake in the white matter but no significant uptake extending in the gray matter, indicating no detectable amyloid deposition.

(Left) More inferior F-18 florbetapir PET in the same patient shows homogeneous uptake in the temporal lobe gray matter; however, the cerebellum maintains a clear distinction between gray and white matter, which is expected even in patients with significant amyloid deposition. Therefore, the cerebellum is used as a reference for gray/white distinction in all patients. (Right) More inferior axial F-18 florbetapir PET in the same patient again demonstrates clear cerebellar gray and white differentiation.
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(Left) Axial F-18 FDG PET in an elderly patient with mild dementia shows AD findings of reduced metabolism in the posterior parietal and frontal cortices. Note normal metabolism in the sensorimotor region.

(Right) Axial F-18 FDG PET in a patient with late-stage AD demonstrates severely reduced metabolism in the posterior parietal and frontal cortices. Note sparing of the sensorimotor region.

(Left) More inferior axial F-18 FDG PET in the same patient shows further evidence of hypometabolism of the posterior parietal and frontal cortices. Importantly, there is normal metabolism in the visual cortex.

(Right) More inferior axial F-18 FDG PET in the same patient shows severe hypometabolism of the posterior parietal and frontal cortices. Note normal metabolism in the visual cortex.

(Left) More inferior axial F-18 FDG PET in the same patient shows hypometabolism of the temporal and frontal cortices. Note normal metabolism in the basal ganglia.

(Right) More inferior axial F-18 FDG PET in the same patient shows severe hypometabolism of the temporal and frontal cortices. Importantly, there is sparing of the basal ganglia.