Introduction and Process
Norman L. Foster, MD

Overview
- An interactive discussion of clinical cases with FDG-PET scans and autopsy diagnosis of Alzheimer's disease (AD) or frontotemporal dementia (FTD)
- Briefly review FDG-PET and its interpretation in dementia
- Briefly review the clinical criteria for AD and FTD
- Briefly review the histopathology of AD and FTD
- Cases will be presented to stimulate discussion
- We will ask the audience to vote on diagnosis

Objectives
- CMS recently approved the use of FDG-PET in the evaluation of dementia to distinguish AD from FTD
- Neurologists need to better understand when and how to utilize this new technology
- Improve accuracy and confidence in clinical diagnosis of dementing illnesses
- Learn when and how to use molecular imaging in dementia evaluations
- Better apply diagnostic criteria for dementing disorders in individual situations

Why FTD and AD?
- AD and FTD are common causes of dementia
  - AD is the most common cause of dementia in the elderly in the US
  - FTD is much less prevalent, but still the second most common neurodegenerative cause early-onset dementia
- Neither has characteristic physical findings that aid the diagnosis of other dementias
- Clinically difficult to distinguish
- FDG-PET can help this clinical decision and is CMS approved

FTD May Mimic AD
- Behavior disturbance is common in AD
- Language is affected early in AD
- AD is sometimes asymmetric causing prominent aphasia
- Most FTD patients develop a significant memory disturbance
- Most FTD patients also meet NINCDS-ADRDA criteria for AD (Varma et al., JNNP 1999;66:184-188)
- Clinicians depend upon relative severity of symptoms; none are pathognomonic
**Clinical Summaries**
- Collected all available medical records
- Removed personal identifiers, imaging results, and autopsy reports
- Several page clinical narrative from these records summarizing the patient’s entire clinical course
- Developed by a dementia expert unaware of diagnosis who did not serve as a rater

**How We Will Consider Cases**
- Review scenario and rate, then we will discuss
- Review with FDG-PET and rate, then discuss with interpretation of FDG-PET
- Present neuropathological findings
- Diagnosis - AD or FTD
  - Must decide one or the other
- Degree of Confidence
  - Very confident
  - Somewhat confident
  - Uncertain

**How to Rate Cases**
- Diagnosis - AD or FTD
  - Must decide one or the other
- Degree of Confidence
  - Very confident
  - Somewhat confident
  - Uncertain

**Rating Card Example**

<table>
<thead>
<tr>
<th>Scenario #</th>
<th>AD</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is your best diagnosis after reviewing? (select only one)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. What is your confidence in this diagnosis? (select only one)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Very confident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Somewhat confident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Uncertain</td>
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</tbody>
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Clinical Application of FDG-PET Imaging
Norman L. Foster, MD

18-F Flurodeoxyglucose Positron Emission Tomography (FDG-PET)
- FDG-PET provides unique information, complementary to structural imaging
- Short-lived positron-labeled form of sugar that follows the early steps of glucose, but gets trapped in the cell
  - Fluorine -18: 120 min
- PET scanner uses physical properties of positrons to localize relevant radioactive emissions and discards others (improved resolution)

What Glucose Metabolism Measures
- Under normal conditions the brain uses glucose as its sole source of energy
- Glucose metabolism primarily reflects synaptic activity
- Hypometabolism may not correspond to areas with greatest changes in routine neuropathology
- Routine neuropathology is better at detecting loss of neuronal cell bodies than synapses
- It is not directly affected by intracellular or extracellular inclusions

Synapses are Lost Before Neurons Die

FDG-PET Image Presentation Methods

Alzheimer’s Disease
Clinical Application of FDG-PET Imaging
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Frontotemporal Dementia

Simple Rules for FDG-PET Diagnosis in this Course

- Alzheimer’s disease
  - Temporoparietal cortex hypometabolism > frontal cortex
  - Posterior cingulate cortex hypometabolic
- Frontotemporal dementia
  - Frontal cortex hypometabolism > temporoparietal cortex
  - Anterior temporal and anterior cingulate cortex hypometabolic
- When several areas affected, are AD or FTD regions most hypometabolic
Clinical Diagnostic Criteria for AD and FTD
Edward Zamrini, MD

Overview
- Clinical features and diagnostic criteria for Alzheimer’s disease
- Clinical features and diagnostic criteria for frontotemporal dementia
- Reasons for difficulty with diagnosis
- Importance of making a diagnosis

Objectives
- Improve accuracy and confidence in clinical diagnosis of dementing illnesses
- Apply diagnostic criteria for dementing disorders in individual situations
- Identify features that distinguish between AD and FTD

Alzheimer’s Disease
- Insidious onset of gradual progressive dementia
- Memory loss usually initial and most prominent symptom
- No focal weakness or sensory loss
- Gait normal and continent until late in the illness
- NINCDS-ADRDA criteria validated

NINCDS/ADRDA
- Criteria for Diagnosis of Probable AD:
  - (a) Dementia established by clinical examination, and documented by a standard test of cognitive function, and confirmed by neuropsychological tests.
  - (b) Significant deficiencies in two or more areas of cognition, for example, word comprehension and task-completion ability.
  - (c) Progressive deterioration of memory and other cognitive functions.
  - (d) No loss of consciousness.
  - (e) Onset from age 40 to 90, typically after 65.
  - (f) No other diseases or disorders that could account for the loss of memory and cognition.

Frontotemporal Dementia
- Insidious onset of progressive dementia
- Disturbing behavior and speech problems most prominent, less evident memory loss
- Perseveration, decreased verbal fluency
- Typical behavioral changes including apathy unrestrained and inappropriate social conduct
- Memory loss often not prominent; AD screening tests may be insensitive
- May be associated with motor neuron disease
Clinical Diagnostic Criteria for AD and FTD
Edward Zamrini, MD

FTD: Clinical profile
- Frontotemporal dementia (FTDbv): Character change and disordered social conduct. Instrumental functions relatively well preserved.
- Progressive nonfluent aphasia (PA): Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well preserved.
- Semantic aphasia and associative agnosia dementia (Semantic dementia, SD): Impaired understanding of word meaning and/or object identity.

Diagnostic features of frontotemporal dementia behavioral variant
- I. Core diagnostic features of FTD
  - A. Insidious onset and gradual progression
  - B. Early decline in social interpersonal conduct
  - C. Early impairment of personal conduct
  - D. Early emotional blunting
  - E. Early loss of insight
- II. Supportive diagnostic features of FTD
  - A. Behavioral disorder
  - B. Speech and language
  - C. Physical signs

Diagnostic features progressive non-fluent aphasia
- I. Core diagnostic features of PA
  - A. Insidious onset and gradual progression
  - B. Nonfluent spontaneous speech with: agrammatism, phonemic paraphasias, anomia
- II. Supportive diagnostic features of PA
  - A. Speech and language
    - 1. Stuttering or oral apraxia
    - 2. Impaired repetition
    - 3. Alexia, agraphia
    - 4. Early preservation of word meaning, 5. Late mutism
  - B. Behavior
    - 1. Early preservation of social skills
    - 2. Late behavioral changes similar to FTD
  - C. Physical signs: late contralateral primitive reflexes, akinesia, rigidity, and tremor

Diagnostic features of semantic aphasia and associative agnosia
- I. Core diagnostic features of SD
  - A. Insidious onset and gradual progression
  - B. Language Disorder and/or
  - C. Perceptual disorder
  - D. Preserved perceptual matching and drawing reproduction
  - E. Preserved single-word repetition
  - F. Preserved ability to read aloud and write to dictation orthographically regular words
- II. Supportive diagnostic features of semantic dementia
  - A. Speech and language
  - B. Behavior
  - C. Physical signs

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AD or FTD Does it Make a Difference?
- YES!!!
- Drug treatment differs
  - In FTD no evidence of a cholinergic deficiency
  - In FTD impaired initiative is easily confused with depression
  - In FTD amyloid strategies are inappropriate
- Management differs
  - In FTD behavior less likely to respond to usual drug treatments and appear to be more spontaneous rather than responsive to environment
  - Understanding behavior can help caregivers
- Prognosis and genetics differ

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Pathological Diagnostic Criteria: An overview of AD and FTD pathology and diagnostic criteria

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VA Northwest Network Mental Illness and Parkinson's Disease Research, Education, and Clinical Centers

Overview:
Neuropathology of AD and FTD

- Review of AD pathology
  - CERAD and Reagan criteria
  - Stains for detection of NP and NFT
- Review of FTD pathology
  - Pathologic subgroups
  - Stains for detection of FTD-associated pathology

Normal Brain Weight
Mean Brain Weight:
1424g for men
1265g for women

Stains for AD/FTD neuropathology

- Histologic stains
  - Bielschowsky (silver stain): NP, NFT, PB, BN
  - LFB/H&E: myelin, neurons, glia
  - PTAH: glia (reactive, fibers)
- Immunohistochemistry
  - tau: NFT, neurites in plaques, PB
  - ubiquitin: NFT, neurites in plaques, PB, LB, "ubiquitin-only" inclusions and neurites
  - neurofilament: NFT, BN

Alzheimer's Disease—Pathology

Auguste Autopsy (1906):
"...evenly affected atrophic brain..."
Bielschowsky stain:
- Axils arranged parallel...a tangled bundle of fibers...
- Dispersed over the entire cortex...miliary foci

(Diagram of Bielschowsky stain)
Alzheimer's Disease (AD)

CERAD Criteria for AD
Neuritic Plaques
- Cortical density of neuritic plaques
  - “Infrequent”
  - “Moderate”
  - “Frequent”
- Classification “possible” or “probable”
  - Interaction of plaque stage and age (A,B,C)
- Neurofibrillary tangles are not considered in these criteria

Neurofibrillary Tangles

Braak Staging of AD
Neurofibrillary tangles

Transentorhinal Stages (I-II)

Limbic Stages (III-IV)

Isocortical Stages (V-VI)


NIA-Reagan Criteria for AD
- Probability pathology accounts for dementia
  - Low-Braak stage I/II, CERAD infrequent plaques
  - Intermediate-Braak stage III/IV, CERAD intermediate plaques
  - High-Braak stage V/VI, CERAD frequent plaques
- Integrates plaque and tangle pathology

Frontotemporal Dementia (FTD)

1892
- Pick describes first case
- 71 y.o. man
- 3 yr decline including aphasia
- Focal temporal lobe atrophy (Chiari)

1911
- Alzheimer describes Pick Bodies (PB) & Ballooned Neurons (BN)

FTD Pathology:
Neuronal loss and gliosis

Normal

FTD

FTD Pathology:
Hippocampal sclerosis

FTD Pathology:
Neuronal and glial alterations

FTD Pathologic Classifications

- **Pick-Type**
  - Severe neuronal loss and gliosis
  - Tauopathy (3R)
  - Pick bodies and ballooned neurons

- **Corticobasal degeneration (CBD)**
  - Tauopathy (4R)
  - NFT, neuropil threads, astrocytic plaques, coiled bodies

- **Progressive supranuclear palsy (PSP)**
  - Tauopathy (4R)
  - NFT, tufted astrocytes, coiled bodies

Mott et al, J Neuropath Exp Neurol, 2005
Review Cases

1) Review Scenario and Vote
2) Review Scenario with PET and Vote
3) Pathology

Scenario 2026

- 61 yo M w 3.5y h/o progressive memory impairment.
- Sx: occ. WFD, poor concentration, difficulty following series of directions, finances, operating power tools. Able to drive.
- SH: Retired billing specialist, 12y ed.
- FH: F w probable dementia
- Neuro: Slight rest and postural tremor of UEs
- MS: MMSE 19. Partly oriented. Trouble naming parts of objects. Impaired WORLD backwards, calculations, clock hands. 0/3 recall, 2/3 with prompting.
- 4y: can’t read, name president, calculate, name items of clothing.
- 4y 9m: Can still travel. May reverse clothing, skips parts of the lawn mowing, unable to start new lawnmower.

Scenario 2026

- 5 y: anxiety & agitation,
- 5y 9m: Cannot roll down car windows, find utensils while eating. Does not speak till spoken to. Unable to speak full sentences.
- 6.5y: brief hallucinations. Easily distracted. Speech limited to 2-word phrases.
- 8y: wandering, occ striking.
- 9y: several falls, complete care, died.

Rate Scenario 2026

1. What is your best diagnosis after reviewing? [Select only one]
   1) Anx
   2) Mixed Stage AD
   3) Frontal Lobe

2. What is your confidence in this diagnosis? [Select only one]
   1) Very confident
   2) Somewhat confident
   3) Unconfident
Rate Scenario with PET 2026

1. What is your best diagnosis after reviewing? (select one only)
   1) AD
   2) TDP

2. What is your confidence in this diagnosis? (Select one only)
   1) Very confident
   2) Somewhat confident
   3) Uncertain

Scenario 2026

- Brain wt 1160g
- Moderate frontal > temporal atrophy

Scenario 2026 - Frontal Cortex
Scenario 2026 - Frontal Cortex

Scenario 2026 - Hippocampus

Scenario 2026 - Hippocampus

Scenario 2026 - Inf. Temporal Gyrus

Scenario 2026
- Brain wt 1160g
- Moderate frontal > temporal atrophy
- Histologic Findings
  - "Frequent" neuritic plaques
  - Braak Stage V
  - No Lewy bodies
  - No Strokes or other focal lesions

2026
- Pathologic Category
  - Definite AD
Scenario 2040

62yo RHF w 2y h/o change in personality and memory loss. Doesn’t participate in daily activities. No longer does housework or participates in conversations, preferring to sit in a chair all day. Stopped driving after becoming lost on familiar routes 1y into her illness. “Very forgetful”. Has purchased items she does not need, and eating more. She may laugh inappropriately or become upset, and has made statements that people are “trying to dupe her”.


At 2y 3mo: speaking less, hums frequently. C’o being tired and hungry all the time. Sleeps frequently during the day. Needs prompting to do household chores and spends most of her day watching TV. On exam, markedly apathetic. Knows date and location. Names current but not prior Presidents. recalls 1/3 after delay. Performed simple but not complex calculations. Excellent naming but occasional paraphasias. Poor comprehension with reading.


6y: no intelligible speech. Agitated, distracted, and may spend time simply staring at her hands. Now needs occasional encouragement to eat. near total care for personal hygiene. On exam, had constant chewing motions. Vocalized with high pitched moans. Frequently attempted to leave the examination room. Frequently clapped. Unable to respond to any commands. Gait slightly slowed and stooped. Grasp reflexes present.

Patient died after 14 years of symptoms.

Rate Scenario 2040

1. What is your best diagnosis after reviewing? (circle only one)
   a) Dementia
   b) Delirium

2. What is your confidence in this diagnosis? (circle only one)
   1) Very confident
   2) Somewhat confident
   3) Uncertain
2040

Rate Scenario with PET 2040

1. What is your best diagnosis after reviewing? (Circle only one)
   1) Dementia
   2) Normal

2. What is your confidence in this diagnosis? (Circle only one)
   1) Very high
   2) Moderate
   3) Normal

Scenario 2040 - Frontal Cortex

Pathologic Category
- Brain wt 800g
- Severe fronto-temporal atrophy
  - "knife-edged" atrophy

Scenario 2040 - FC vs OC

LFB
Bielschowsky
Scenario 2040

- Brain wt 800g
- Severe fronto-temporal atrophy
  - “knife-edged” atrophy
- Histopathology
  - Severe FC/TC neuronal loss and gliosis
  - Pick body inclusions (tau positive)

2040

- Pathologic Category
  - Frontotemporal Dementia
  - Pick’s Disease subtype

Scenario 2162

Review Scenario 2162

- 80 yoF w 6y h/o progressive memory loss. Got lost after taking a bus downtown. Calls D several times a day w/o realizing she had called. Able to shop and prep light meals. Signif. visual and auditory impairment and bumps into objects when walking. She can no longer read or quilt.
- SH: Unknown
- FH: Unknown
- MS: A+O to yr, season, and mo but not day of week. O to place, x county. Recalls 1/3 after 3'. Unable to subtract 7 from 100 and only 3 letters correct when spelling WORLD backwards. No difficulty with language. Mild impairment when copying a design.
- Neuro: Unremarkable x for macular degeneration and auditory impairment.

Scenario 2162

At 6y 9m: in NH, socializes, good mood, incontinent of urine +/- stool. D/o to date & names of children & current events. Follows simple commands. 0/3 recall at 5', 2/3 w clues. Fluent.

At 7y 3m: can feed self, but needs help with dressing, incontinent, calm. O to city and “doctor’s office”. Fluent. 0/3 recall at 5’. Slight stoop.

At 7y 9m: wanders, paces, assists others as possible, helping them get out of restraints.

Patient died after 10.5 years of symptoms.

Rate Scenario 2162

1. What is your best diagnosis after reviewing? (choose only one)
   - [ ] Dementia
   - [ ] Normal cognition
   - [ ] Unravel

2. What is your confidence in this diagnosis? (choose only one)
   - [ ] Very confident
   - [ ] Fairly confident
   - [ ] Unravel
Rate Scenario with PET 2162

1. What is your best diagnosis after reviewing? (circle only one)
   1) AD
   2) PDD

2. What is your confidence in this diagnosis? (circle only one)
   1) very confident
   2) somewhat confident
   3) uncertain

Scenario 2162

- Brain wt 925g
- Severe bilateral fronto-temporal atrophy

Scenario 2162 - Frontal Cortex
Scenario 2162

- Brain wt 925g
- Severe fronto-temporal atrophy

Histopathology:
- Severe neuronal loss and gliosis, insular and temporal cortex, hippocampus ("hippocampal sclerosis"); and substantia nigra
- Ubiquitin-only inclusions/neurities DG, superficial neocortex
- "Frequent" neuritic plaques
- Braak stage III

2162

Pathologic Category - FTD

Frontotemporal Dementia:
Motor Neuron Disease/MND-like Inclusions Subtype

“Intermediate” Likelihood AD