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)
- Review FDG-PET and its interpretation in dementia
- Review clinical criteria for AD and FTD
- Review the histopathology of AD and FTD
- Present cases for discussion
- Ask the audience to vote on diagnosis

Objectives
- Medicare reimburses FDG-PET for dementia only to distinguish AD from FTD
- Neurologists need to better understand when and how to utilize this technology
- Better apply diagnostic criteria for dementing disorders in individual patients
- Improve accuracy and confidence in determining the cause of dementia

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

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 under age 60 probably the second most common neurodegenerative cause of dementia
- Neither has characteristic physical findings that aid the diagnosis of other dementias
- Clinically difficult to distinguish
- FDG-PET can help make this clinical decision
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How We Will Consider Cases
- Review scenario, vote, then discuss
- Review with FDG-PET, vote then discuss
- Present neuropathological findings
- Tabulate vote and post results on the web

Voting Card Example

1. What is your best diagnosis after reviewing? (circle only one)
   1) Dementia
   2) Normal
   3) Somewhat atypical
   4) Uncertain

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

www.utahmemory.org (for students tab)
Clinical Application of FDG-PET Imaging
Norman L. Foster, M.D.

18-F Fluorodeoxyglucose 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
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

CLINICAL DIAGNOSTIC CRITERIA FOR AD AND FTD
Edward Zamrini M.D.
Center for Alzheimer’s Care Imaging and Research
Department of Neurology
University of Utah

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

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

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
FTD: Three Clinical profiles
- Frontotemporal dementia behavioral variant (FTDbv): Personality change, disordered social conduct. Instrumental functions relatively well preserved.
- Progressive nonfluent aphasia (PA): Expressive language deficit is the dominant feature initially and throughout the illness. Otherwise cognition 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

FTD May Mimic AD
- Criteria are subjective and must be interpreted
- AD more prevalent than FTD, especially age >65
- Behavior disturbance also common in AD
- AD is sometimes asymmetric causing prominent aphasia
- Most patients with FTD eventually develop a significant memory disturbance
- Most patients with FTD also meet NINCDS-ADRDA criteria for AD (Varma et al. JNPP 1999:66:184-188)
- Clinicians depend upon relative severity of symptoms; none are pathognomonic
Pathological Diagnostic Criteria:
An overview of AD and FTD pathology and diagnostic criteria
James B. Leverenz, MD

Overview:
Neuropathology of AD and FTD

- Review of AD pathology
  - Stains for detection of NP and NFT
  - CERAD and Reagan criteria

- 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

Alzheimer's Disease (AD)

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CERAD Criteria for AD
Neuritic Plaques
- Density of neocortical neuritic plaques
  - “Infrequent”
  - “Moderate”
  - “Frequent”

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)
Pathology: Neuronal loss and gliosis
- Normal
- FTD

FTD Pathology:
Hippocampal sclerosis
- DG
- CA-1
- PHG

FTD Pathology:
Neuronal and glial alterations
- Pick Bodies (PB)
- Ballooned Neuron (BN)

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**Pathological Diagnostic Criteria:**
An overview of AD and FTD pathology and diagnostic criteria
James B. Leverenz, MD

**FTD Pathology:**
Neuronal and glial alterations

- Ubiquitin-only inclusions
- Tau-positive glial inclusions

**FTD Pathologic Classifications**

- **Pick-Type**
  - Severe neuronal loss and gliosis
  - Tautopathy (3R)
  - Pick bodies and balloononed neurons

- **Frontotemporal lobar degeneration with MND or MND-type inclusions (FTLD-MND/MNI)**
  - Variable neuronal loss and gliosis
  - "ubiquitin-only" inclusions (TDP-43+)

- **Dementia lacking distinctive histopathology (DLDH)**
  - Neuronal loss and gliosis without distinctive biochemical signal (e.g. tau or ubiquitin-only pathology)

**Other Tauopathies**

- Neurofibrillary tangle dementia (tau mutations)
- Corticobasal degeneration (4R tauopathy)
- Progressive supranuclear palsy (4R tauopathy)

- There is some incongunity between clinical and neuropathological subtypes of FTD

*Mott et al, J Neuropath Exp Neurol, 2005*
Case Scenarios
Faculty (Norman L. Foster, MD, Edward Zamrini, MD, James B. Leverenz, MD)

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

Scenario 2026
- 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.

Rate Scenario 2026

1. What is your best diagnosis after reviewing? (Circle only one)
   (A) (B) (C) (D) (E)

2. What is your confidence in this diagnosis? (Circle only one)
   (A) (B) (C) (D) (E)

2026

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2026

Rate Scenario with PET 2026

1. What is your best diagnosis after reviewing? (choose only one)
   
   1) AD
   2) PD
   3) Other

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

Scenario 2026

☐ Brain wt 1160g
☐ Moderate frontal > temporal atrophy

Scenario 2026 - Frontal Cortex

normal thickness, plaques visible

Scenario 2026 - Frontal Cortex

plaques and tangles visible

Scenario 2026 - Hippocampus

plaques visible in CA1

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Scenario 2026 – Hippocampus
- plaques and tangles visible in CA1

Scenario 2026 - Aβ and tau
- Frontal Cortex - Aβ
- Frontal Cortex - tau

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

Scenario 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".

Scenario 2040
- 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.
Scenario 2040

- 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? Select only one.
   - Select all that apply.
   - 1) Very confident
   - 2) Somewhat confident
   - 3) Uncertain

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

Scenario 2040

- Brain wt 800g
- Severe fronto-temporal atrophy
  - "knife-edged" atrophy
Case Scenarios
Faculty (Norman L. Foster, MD, Edward Zamrini, MD, James B. Leverenz, MD)

Scenario 2040 - Frontal Cortex
marked frontal cortical thinning and gliosis, no plaques

Scenario 2040 - FC vs OC
relative sparing of thickness and architecture in OC

Scenario 2040 - Frontal Cortex
gliosis and severe neuronal loss

Scenario 2040 - Frontal Cortex
tau positive Pick bodies

Scenario 2040 – Hippocampus
tau positive Pick bodies in CA1 and DG

Scenario 2040 - Dentate Gyrus
3R tau positive, 4R tau and TDP-43 negative
Case Scenarios
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Scenario 2040
- Brain wt 800g
- Severe fronto-temporal atrophy
  - "knife-edged" atrophy
- Histopathology
  - Severe FC/TC neuronal loss and gliosis
  - Pick body inclusions
  - 3R tau positive, 4R tau and TDP-43 negative

Pathologic Category
Frontotemporal Dementia
Pick’s Disease subtype

Scenario 2178
- 59 yo M, 1.5y h/o memory loss.
- Sx: Trouble w names, incl. his children, bus driver routes (laid off), recalling conversations.
- SH: College degree in industrial arts.
- FH: M w dementia, age 84. Possible memory loss in F in late 70’s.
- MS: O x3/3, slight halting speech, 0/3 recall, 2/3 w significant prompting. Poor calc, FOK. Concrete. Boston naming 14/60
- Neuro: +snout, +glab, tr. Suck. - grasp, - palmo-mental

Scenario 2178
- 2y: 0/3 recall. DS 5F, 4R. +WFD.
- 3.5y: Does not recognize family members by name. difficulty w chores. No longer reads. Got lost walking.
- 4y 3m: Frequent arising at night. Helps less w housework. D/o to age, place. Cannot name objects or body parts.
- 5y: Will lick the dishes at a restaurant. Tried to kiss examiner.
- 5.5y: urinates in public & attempts fondling. Physically abusive. Day/night confusion. Does not recognize wife
- 8.5y: died.

Rate Scenario 2178
1. What is your best diagnosis after reviewing? (Circle only one)
   1) 3R tau
   2) 4R tau
   3) TDP-43
   4) Pick’s
   5) Other

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

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Rate Scenario with PET 2178
1. What is your best diagnosis after reviewing? (circle only one)
   1) AD
   2) VaD
   3) Another
   4) Uncertain

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

Scenario 2178
- Brain wt 1035
- Right medial temporal lobe atrophy

Scenario 2178 - Frontal Cortex
- Mild frontal cortical thinning, no plaques

Scenario 2178 - Frontal Cortex
- Ubiquitin and TDP-43 positive inclusions and neurites

Scenario 2178 - Hippocampus/PHG
- CA-1 and Parahippocampal gyrus thinning

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Scenario 2178 - Hippocampus/PHG
severe neuronal loss and gliosis in PHG

Scenario 2178 - Dentate Gyrus
ubiquitin positive, tau negative inclusions

Scenario 2178 – Striatum
neuronal loss and gliosis, TDP-43 positive inclusions

Scenario 2178

- Brain wt 1035
- Right medial temporal lobe atrophy
- Histopathology
  - Severe temporal cortical and striatal neuronal loss and gliosis (relative sparing of frontal lobe)
  - Ubiquitin and TDP-43 neuronal inclusions and neurites in neocortex, dentate gyrus, striatum
  - Mild neuronal loss in hippocampus and substantia nigra

Pathologic Category - FTD

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

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