Multimodality Dementia Imaging

Saeed Elojeimy MD, Phd
Chief of Nuclear Medicine
Department of Radiology
University of New Mexico
1. Discuss role of cross sectional imaging in the evaluation of dementia

2. Overview of nuclear imaging tools in evaluation of dementia

3. Review molecular imaging patterns for anterior and posterior dementia syndromes

4. Highlight through clinical cases evolving role of PET imaging in evaluation of PPA and dementia associated movement disorders
Dementia Workup

Clinical Evaluation

Cross Sectional Imaging

Molecular Imaging

Correlation of clinical symptoms and imaging findings is the best approach to reach a unified and accurate diagnosis and to avoid diagnostic pitfalls.
Role of Cross-Sectional Imaging in Dementia

- American Academy of Neurology Practice Parameter recommends using anatomical imaging computed tomography (CT) or magnetic resonance imaging (MRI) to rule out reversible treatable causes.

- MRI Brain is usually better than CT (which tends to be used more in acute settings).

(A) Axial section through fluid-attenuated inversion recovery image from a patient with vascular dementia, showing multiple patchy areas of high signal in periventricular white matter (arrows). (B) Coronal gradient echo MR image showing multiple microhemorrhages (arrowheads).

Axial diffusion-weighted imaging showing cortical ribboning (arrows), left more than right, in a patient with Creutzfeldt–Jakob disease.

Normal Pressure Hydrocephalus

Axial CT (left) and MRI T2 sequence (right) images showing markedly dilated ventricles in the setting of NPH
In advanced neurodegenerative syndromes, cross-sectional imaging may reveal anatomic changes and areas of brain atrophy.

Axial FLAIR MR shows frontal lobe volume loss, as well as associated hyperintense signal in white matter in a patient with FTLD.

Axial T2WI MR through the inferior temporal lobes shows marked atrophy of temporal lobes and enlargement of parahippocampal fissures in a patient with Alzheimer’s.

Axial T2 MR in a 71-year-old male with corticobasal degeneration demonstrates asymmetric atrophy and thin cortex in the left perirolandic region in a patient with CBD.
Examples of the visual rating scale for the medial and lateral temporal lobe on MR coronal images displayed conventionally with the letter on the right. This scale rates 0=normal, 1=minimal atrophy, 2=moderate atrophy, and 3=severe atrophy (see arrows); (A) normal medial and lateral temporal lobe structures (rated 0 bilaterally); (B) minimal atrophy of medial temporal lobe structures (rated 1 bilaterally); (C) severe medial and lateral atrophy on the right (graded 3) and moderate on the left (graded 2).
**MRI SPECTROSCOPY:** Neuronal damage by comparing NAA (neuronal marker) over myoinositol peak in Alzheimer’s versus control patients

![Figure 1](image1.png)

*Figure 1. 1H MR spectroscopy (1H MRS) in the clinical evaluation of a patient with Alzheimer’s disease (AD). The graphic at the top is an example of 1H MRS at the posterior cingulate of a normal volunteer. Below, find an example of 1H MRS of a patient with AD. Note the reduction of N-Acetylaspartate (NAA) and increase of myoinositol (mI) peaks.*

**DIFFUSION TENSOR IMAGING:** uses fractional anisotropy measurements to detect white matter degradation

![Figure 2](image2.png)


Finding pathology on structural imaging should not preclude molecular imaging to exclude other coexistent pathology

1. Multiple studies has established that there is an overlap between the clinical symptoms and imaging findings of normal pressure hydrocephalus (NPH) and other neurodegenerative diseases. Specifically, Alzheimer’s was found in a significant proportion of patients clinically diagnosed with NPH.


3. Similarly Alzheimer’s disease may coexist with other pathologies such as vascular dementia, HIV dementia, and amyloid angiopathy.

Overview of Nuclear Neuroimaging tools

SPECT
Tracers: Tc-99m HMPAO, Tc-99m ECD
Mechanism of uptake: cerebral perfusion
Clinical significance: cerebral perfusion is decreased in brain regions responsible for dementia

FDG-PET
Tracer: 18F-FDG
Mechanism of uptake: cerebral glucose metabolism
Clinical significance: cerebral metabolism is decreased in brain regions responsible for dementia

## Overview of Nuclear Neuroimaging tools

**SPECT**
- Tracers: Tc-99m HMPAO, Tc-99m ECD
- Mechanism: cerebral perfusion and metabolism are coupled with neuronal activity
- Clinical significance: cerebral perfusion is decreased in brain regions responsible for dementia

**FDG-PET**
- Tracer: 18F-FDG
- Mechanism: indicator of cerebral glucose metabolism
- Clinical significance: cerebral metabolism is decreased in brain regions responsible for dementia

**DaTscan**
- Tracer: ioflupane iodine-123
- Mechanism: detects dopamine pre-synaptic transporters
- Clinical Significance: decreased dopamine transporters are seen with nigrostriatal degeneration, indicative of Parkinson’s disease or Parkinson Plus syndrome

**Amyloid Imaging**
- Tracer: C11-Pib, F-18 florbetapir; F-18 flutemetamol; F-18 florbetaben.
- Mechanism: detects amyloid deposition
- Clinical Significance: increased amyloid deposition is seen in Alzheimer’s disease
Anterior Dementia
FTLD can be further divided into three clinical subtypes depending on perfusion imaging findings:

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Distribution</th>
<th>Other PET / SPECT Findings</th>
<th>NGD (DaT)</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal Dementia</td>
<td>Anterior (Frontotemp)</td>
<td>-</td>
<td>-</td>
<td>Personality and behavioral changes, Language problems, early age (50-60)</td>
</tr>
</tbody>
</table>

Case in Point 1

80 year old psychiatrist with 3 years of cognitive changes, word finding difficulty, and short term memory problems.
Bi-temporal lobe hypometabolism, most compatible with semantic dementia (temporal lobe predominant FTD).
Axial SPECT images (top) and 3D-SSP reconstruction (bottom) following injection of Tc-99m ECD show moderate decreased uptake in bilateral anterior temporal lobes in the setting of prior head injury consistent with TBI.
Chronic depression and chronic alcohol abuse may cause frontal hypometabolism/hypoperfusion.

60 year old female with major depression and cognitive impairment. Axial SPECT perfusion images show pronounced decreased perfusion of anterior frontal lobes (arrows). Even though findings are compatible with FTD, depression can also be contributing to hypoperfusion of frontal lobes. A follow-up exam after depression control could be helpful, as depression induced hypoperfusion tends to be reversible.

# Anterior Dementia Motor Variants

<table>
<thead>
<tr>
<th></th>
<th>Distribution</th>
<th>Other PET / SPECT Findings</th>
<th>NGD (DaT)</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Motor Sx</strong></td>
<td>FTLD</td>
<td>Anterior (Frontotemp)</td>
<td>-</td>
<td>Personality and behavioral changes, Language problems, early age (50-60)</td>
</tr>
<tr>
<td><strong>With Motor Sx</strong></td>
<td>PSP</td>
<td>Anterior (Frontotemp)</td>
<td>Midbrain, Thalamus, +</td>
<td>Parinaud, extra-pyramidal Sx</td>
</tr>
<tr>
<td></td>
<td>CBD</td>
<td>Anterior (Frontopariet)</td>
<td>sensorimotor cortex, very asymmetric, +</td>
<td>Alien hand syndrome, extra-pyramidal Sx.</td>
</tr>
</tbody>
</table>

**Teaching Pearl:** Dat Scan Imaging is typically positive in anterior dementia syndromes with motor symptoms.

FT: Frontotemporal hypoperfusion / hypometabolism

ALS is another Anterior Dementia
Case in Point 2

A 54-year-old woman presented with rapidly progressing rigidity, bradykinesia, abnormal neck postures, gait disturbance, bulbar dysfunction (swallowing difficulty), and no overt cognitive deficit at the time of imaging.

99mTc-HMPAO SPECT (A) at 22 months post onset of the symptoms showed mild to moderate hypoperfusion in the lateral and medial frontal association cortices bilaterally and mild hypoperfusion involving the right thalamus and right putamen (arrows).

123I-FP-CIT SPECT (A) showed severely decreased uptake in the right putamen and mild reduction in the posterior portion of the left putamen and in the left and right caudate.

Fused axial and sagittal SPECT (top) and 3D-SSP (bottom) images following injection of Tc-99m HMPAO show decreased perfusion to the frontal and temporal lobes, and the upper brainstem (arrows), consistent with progressive supranuclear palsy.
FDG PET-CT showing severe asymmetrical right hemisphere hypometabolism with involvement of the right sensorimotor cortex in a case of corticobasal degeneration.
Posterior Dementia
### Posterior Dementia

<table>
<thead>
<tr>
<th>Distribution</th>
<th>PET / SPECT Findings</th>
<th>Nigrostriatal Degeneration (DaT)</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>Posterior PT¹</td>
<td>-</td>
<td>Memory loss, Poor judgement/ decision making</td>
</tr>
<tr>
<td>Dementia of Lewy Body</td>
<td>Posterior PT + Medial Occipital lobe</td>
<td>+</td>
<td>Visual hallucinations, EPS</td>
</tr>
</tbody>
</table>

**Teaching Pearl:** Dat Scan Imaging is typically positive in Dementia of Lewy body

¹PT: Parieto-Temporal hypoperfusion / hypometabolism
Decreased perfusion of the posterior cingulate gyrus on SPECT is the earliest change seen in AD (case on right).

Sagittal SPECT perfusion images in a patient with cognitive impairment and memory loss showing decreased perfusion in the posterior cingulate gyrus (arrow) consistent with early Alzheimer’s disease.

Elevated fasting blood glucose (with effects noted above FBG 110) may cause false positive hypometabolism in precuneus and posterior cingulate: an Alzheimer’s mimick.

Clinical Pearl: Involvement of the medial occipital lobes differentiates DLB from AD.

DaT scan is helpful to differentiate challenging cases of AD versus DLB.

B-amyloid Imaging: Brief Overview
Beta-amyloid Imaging

In negative scans, gray matter shows less cortical radioactivity than does the adjacent white matter, preserving clear borders between the two areas. But in positive scans, gray-white contrast drops, and cortical radioactivity is more similar—or even exceeds—that of the nearby white matter. *Image credit: Eli Lilly and Company*
11C-PiB, 18F-florbetaben, 18F-florbetapir, and 18F-flutemetamol images of healthy subjects and AD patients. Christopher C. Rowe, and Victor L. Villemagne J Nucl Med 2011;52:1733-1740
Amyloid imaging is a helpful tool to differentiate FTLD from Alzheimer’s.

Negative scan excludes Alzheimer (high NPV for Alzheimer).

---

Prevalence of Amyloid PET+ in Dementia Syndromes

- AD: Alzheimer’s disease
- PCA: Posterior cortical atrophy
- LPA: Logopenic aphasia
- FTD: frontotemporal dementia
- SD: Semantic dementia
- PNFA: Progressive non-fluent aphasia
- bvFTD: (behavioral variant) frontotemporal dementia
- VaD: Vascular dementia
- DLB: Dementia with Lewy bodies
- PDD: Parkinson’s disease dementia
- CBS: Corticobasal syndrome

Ossenkoppele et al., JAMA 2015
Figure Legend:

Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status. The prevalence estimates were generated from generalized estimating equations. The model included age and cognitive status as predictors. Shading indicates 95% CIs; SCI, subjective cognitive impairment; MCI, mild cognitive impairment.

PPV of amyloid imaging for diagnosing Alzheimer dementia decreases with age.
Appropriate Use Criteria for Amyloid PET per SNM and Alzheimer’s society guidelines: Indications that are SUPPORTED

• Atypical Early age Onset (less than 65), especially if PET findings are confusing and want to differentiate FTLD from Alzheimer

• Persistent / Progressive unexplained MCI
Appropriate Use Criteria for Amyloid PET per SNM and Alzheimer’s society guidelines: Indications that are NOT SUPPORTED

- Differentiate Alzheimer from DLB
- Determine Dementia severity
- Confirm Alzheimer in setting of a typical parieto-temporal distribution on PET
- Screening of cognitive normal patients
- Use scan findings to support disability
- Screen family members

Johnson et. al 2015
Frontal variant Alzheimer's disease

Clinical Pearl: Amyloid Imaging is helpful to differentiate Frontal variant AD from FTD.

Laforce and Rabinovici Alzheimer’s Research & Therapy 2011, 3:31
Posterior Cortical Atrophy (Alzheimer’s variant)

62-year-old woman with visuospatial dysfunction.

Simultagnosia

Role of PET for imaging of PPA and dementia associated with movement disorders
68 yo cosmetologist presents with language problems and aphasia, specifically trouble with word repetition. Rule out FTD. Outside hospital MRI raised possible vascular etiology.
What is the most likely diagnosis?

1. Fronto-temporal dementia
2. Posterior Cortical Atrophy
3. Dementia of Lewy Body
4. Leucopenic Progressive Atrophy
What is the most likely diagnosis?

1. Fronto-temporal dementia
2. Posterior Cortical Atrophy
3. Dementia of Lewy Body
4. Leucopenic Progressive Atrophy (alzheimer’s variant)
Figure 2. Voxel-level imaging findings in IvPPA and DAT when compared to controls. Three dimensional renderings show regions of reduced FDG metabolism and gray matter (GM) volume in IvPPA compared to controls and in DAT compared to controls. All images were generated using an FDR corrected statistical threshold of $p<0.0005$ and an extent threshold of 100 voxels. A decrease in brightness of the render reflects increased distance from the surface of the tissue.

doi:10.1371/journal.pone.0062471.g002
<table>
<thead>
<tr>
<th>Clinical Association</th>
<th>Pathology</th>
<th>Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Semantic (Fluent)</strong></td>
<td>FTLD</td>
<td>Tau positive pathology</td>
</tr>
<tr>
<td><strong>Nonfluent</strong></td>
<td>FTLD</td>
<td>ubiquitin-positive, TDP43-positive pathology</td>
</tr>
<tr>
<td><strong>Logopenic</strong></td>
<td>Alzheimer’s disease</td>
<td>PET-PIB positivity and decreased A 42 and increased tau in the CSF</td>
</tr>
</tbody>
</table>
Results of the region of interest analysis in the insulae with Voxel based morphometry (VBM). Statistical significance of loss of gray matter in the insula in nfvPPA compared to bvFTD are shown in red. Statistical significance of loss of gray matter in the insula in bvFTD compared to nfvPPA are shown in blue. Results are at p<0.001 without correction for multiple comparisons.

Clinical tasks used to assess speech and language functions in PPA

<table>
<thead>
<tr>
<th>Speech/language function</th>
<th>Task</th>
<th>Behavioral measures</th>
<th>Variant in which impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech production</td>
<td>Picture description task; story retelling (e.g., picture aided); constrained-syntax sentence production task</td>
<td>Grammatical structure; mean length of utterance; speech rate; accuracy of content; melody; prosody; specific error types in word selection; articulation</td>
<td>Nonfluent/agrammatic variant</td>
</tr>
<tr>
<td>Motor speech</td>
<td>Motor speech evaluation, including multiple repetitions of multisyllabic words; diadochokinesis of speech articulators; spontaneous speech</td>
<td>Effortfulness; hesitations; presence of apraxia of speech or dysarthria; specific types of speech sound errors; factors that affect articulation (e.g., word length in syllables)</td>
<td>Nonfluent/agrammatic variant</td>
</tr>
<tr>
<td>Confrontation naming</td>
<td>Single-word retrieval in response to pictures, sounds, foods, and odors</td>
<td>Error rate; delay in naming; factors that affect naming accuracy (e.g., familiar vs unfamiliar items, nouns vs verbs, semantic category); error types (e.g., semantic errors, phonemic errors)</td>
<td>Severe deficit in semantic variant with semantic errors; moderate impairment in logopenic variant with phonemic errors</td>
</tr>
<tr>
<td>Repetition</td>
<td>Oral repetition of words, pseudowords, phrases, and sentences</td>
<td>Factors that affect repetition accuracy (e.g., predictability of the phrase, sentence length, grammatical complexity); error types</td>
<td>Logopenic variant with phonological errors</td>
</tr>
<tr>
<td>Sentence comprehension</td>
<td>Matching orally presented sentences to pictures; answering yes/no questions; following directions</td>
<td>Factors that affect comprehension (e.g., grammatical complexity; reversibility of the sentence, e.g., The boy was kicked by the girl vs The ball was kicked by the girl)</td>
<td>Nonfluent/agrammatic variant, effect of grammatical complexity; logopenic variant, length and frequency effect</td>
</tr>
<tr>
<td>Single-word comprehension</td>
<td>Word-to-picture matching; Word-to-definition matching; Synonym matching</td>
<td>Factors that affect comprehension (e.g., familiarity; frequency; grammatical word class)</td>
<td>Semantic variant</td>
</tr>
<tr>
<td>Object/people knowledge</td>
<td>Picture-picture matching; odd-one-out; semantic associations; gesture-object matching; sound-picture matching</td>
<td>Factors that affect object knowledge (e.g., familiarity, semantic category)</td>
<td>Semantic variant</td>
</tr>
<tr>
<td>Reading/spelling</td>
<td>Lists including regular and irregular word lists, from various word classes, matched for other factors; pseudowords matched to words in length</td>
<td>Factors that affect reading/spelling accuracy (e.g., regularity, frequency, word class); error types (e.g., regularization, phonologically plausible errors; articulatory distortions)</td>
<td>Semantic variant with &quot;regularization&quot; errors; logopenic variant phonologic errors</td>
</tr>
</tbody>
</table>
Many patients with non-fluent aphasia will eventually progress to an encompassing generalized motor problem compatible with a diagnosis of corticobasal syndrome or progressive supranuclear palsy.

Diagnosis of PPA is preserved for patients in which aphasia is the predominant symptom.

FDG Brain PET-CT is increasingly being used in primary progressive aphasia for appropriate classification and specifically to differentiate FTLD from Alzheimer’s pathology since this affects clinical management and treatment.
Case in Point 4:

60 year old male with established long history of Parkinson’s disease presenting with dementia symptoms
What is the most likely diagnosis?

1. Posterior Cortical Atrophy
2. Alzheimer’s dementia
3. Leucopenic Progressive Atrophy
4. Dementia of Lewy Body
5. Parkinson’s Dementia
What is the most likely diagnosis?

1. Posterior Cortical Atrophy
2. Alzheimer’s dementia
3. Leucopenic Progressive Atrophy
4. Dementia of Lewy Body
5. Parkinson’s Dementia

**1-year rule:** patients with L-Dopa responsive parkinsonism who develop dementia more than 1 year after their initial PD motor symptoms are classified as PDD.

Figure 1. Metabolic reduction in Parkinson’s disease 3D-SSP t-statistic maps comparing PD dementia nonconverters and converters based on voxel-based comparison to normative data from healthy controls at baseline. The most prominent metabolic reduction in the prospective PDD converters is evident in the cuneus (especially Brodmann area 18) and precuneus. Mild-to-moderate reductions are also present in the mesiofrontal lobes. In addition, the PD dementia converter subjects demonstrate relative sparing of the primary sensorimotor cortex, a pattern similar to Alzheimer’s disease. In PD nonconverter subjects, metabolic reduction in the posterior calcarine cortex (Brodmann area 17) is evident, while there is relative sparing of Brodmann areas 18, 19 and the precuneus.

LLAT: Left lateral; LMed: Left medial; PD: Parkinson’s disease; PDD: Parkinson’s disease with dementia; RLAT: Right lateral; RMED: Right medial.
Summary

• Reviewed the role of cross-section structural imaging in evaluation of dementia (typically MRI preferred to exclude rare reversible causes of dementia).
• Reviewed the patterns of hypoperfusion / hypometabolism in anterior and posterior dementia subtypes, motor variants, and mimics.
• Illustrated role of DaT scan, and amyloid imaging in troubleshooting challenging diagnoses of neurodegenerative disorders.
• Discussed evolving role of PET imaging in setting of PPA and movement disorders associated dementia.
THANK YOU