Molecular Imaging of Dementia

Matthew L Hemming, PhD
Harvard Medical School Year III
Gillian Leiberman, MD

July 2010
Agenda

1. Introduction to dementia

2. Examples of imaging dementia

3. Alzheimer’s disease overview

4. PiB-PET imaging in Alzheimer’s disease
Dementia Overview

Abbreviated definition: the development of cognitive defects manifested by impairment of memory, social or occupational function and a significant decline from previous levels of functioning.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>60-70</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>20-30</td>
</tr>
<tr>
<td>Other Neurodegenerative</td>
<td>~5</td>
</tr>
<tr>
<td>Non-Neurodegenerative &amp; Non-Vascular</td>
<td>~5</td>
</tr>
</tbody>
</table>

Early onset and late onset forms of dementia exist.
The **Mini Mental Status Exam (MMSE)** is the most widely used dementia screening tool. More extensive neuropsychiatric testing enhances the dementia diagnosis but is not always available.

Physical exam and lab testing are used to exclude other causes of dementia, but this is often the extent of clinical investigation.

Neuroimaging in dementia is currently controversial, with MRI being able to identify atrophy and help differentiate structural, cerebrovascular and metastatic causes of dementia.
Let’s look at a few patient presentations to illustrate the utility of imaging in dementia and conditions of altered mental status.
Patient 1  This 76 year old male presents with agitation, confusion, paranoia and an inability to recognize family members. He has a 100 pack-year smoking history.

Diagnosis: Small Cell Lung Cancer with brain metastasis

Note the contrast enhancing metastatic lesions
Patient 2  This 64 year old male had Follicular Non-Hodgkin Lymphoma and received a bone marrow transplant. He developed mental status changes after treatment with cyclophosphamide.

Initial Presentation

7 Days after drug cessation

Note the posterior and periventricular lesions that improve after drug cessation

*Diagnosis: Posterior Reversible Encephalopathy Syndrome (PRES)*
Patient 3, CT Scan  This 80 year old male presented with an acute onset of dizziness, nausea and vomiting. History is significant only for hypertension.

Initial CT scan reveals cerebellar hemorrhage (arrow).

An MRI was performed to probe for possible masses or regions of infarction.
Patient 3, MRI Imaging: MRI revealed atrophy, foci of hemorrhage in the basal ganglia, thalamus, subcortical white matter & cerebellum.

Diagnosis: Amyloid Angiopathy

Note the multiple hemorrhagic foci prominent on the magnetic susceptibility scan.
Patient 4, MRI This 95 year old female has a history of diabetes, hypertension and a clinical diagnosis of Alzheimer’s disease. MRI shows cerebral atrophy. She presented with an acute onset of dysarthria, inability to follow commands and right-sided hemiparesis.

MRI, T1, no contrast, axial plane

Note the mild cerebral atrophy
Patient 4, CT  A CT perfusion scan revealed decreased perfusion of the left middle cerebral artery and internal carotid artery.

Note the lack of perfusion to the left hemisphere and the MCA occlusion

*Diagnosis: Cerebrovascular Disease*
1) There are diverse causes of dementia, including neurodegenerative, vascular, neoplastic, inflammatory, traumatic, metabolic, infectious, epileptic, prion, congenital and drug-related. The clinical presentation often overlaps, and several imaging modalities are helpful as diagnostics.

2) The majority of dementia cases are difficult to diagnose with certainty prior to autopsy, and current radiologic imaging is of modest diagnostic utility in many dementia-causing conditions.

3) The development of additional non-invasive imaging tools can improve the diagnostic certainty of dementia, and would be useful for clinical research, drug trials and selecting appropriate treatment regimens.
Why have radiologic, biological and other diagnostic assays not yet been developed for many causes of dementia?

There is inherent difficulty in assaying the central nervous system (e.g. biopsy).

The lack of therapeutic options available to patients has historically decreased interest in developing better diagnostic tools.
Alzheimer’s disease, the most common form of dementia, arises from the accumulation of neurotoxic amyloid within the brain.
Over 4 million people suffer from Alzheimer’s disease in the United States, and over 30 million are estimated to be affected worldwide. Costs exceed $148 billion in the US alone.

Alzheimer’s disease prevalence increases with advancing age, affecting approximately 50% of the population at age 85. This pattern is explained by the insidious accumulation and deposition of the neurotoxic amyloid-beta peptide (Aβ).
At the molecular level, Aβ is generated from the amyloid precursor protein by sequential proteolytic cleavage events. There are three possible fates of Aβ:

1. Degradation
2. Transport
3. Aggregation

Aggregation of Aβ into insoluble fibrils forms the characteristic pathologic finding in Alzheimer’s disease: amyloid plaques.
Diagnosis of Alzheimer’s Disease

Clinical diagnosis is based upon symptoms, neurologic exam and tests to exclude other causes (e.g. B12 deficiency). Definitive diagnosis is obtained only at autopsy, which reveals characteristic amyloid plaque deposition visualized by immunohistochemistry or thioflavin staining.
With an understanding of Alzheimer’s disease pathogenesis, radiologic tools may be developed to specifically image amyloid pathology.
To develop an imaging tool that can recognize amyloid, penetrate the blood brain barrier, have favorable pharmacokinetics, and bear a radionuclide for imaging, investigators began by modifying thioflavin’s structure.
Pittsburgh Compound B (PiB), based upon the structure of thioflavin, retains the ability to bind fibrillar amyloid. Incorporated into its structure is a carbon-11 atom, which allows its visualization via positron emission tomography (PET).
Now we’ll consider PET imaging and how PiB can be used to label amyloid plaques in Alzheimer’s patients.
Basics of PET Imaging

A positron-emitting radionuclide tracer accumulates in tissues of interest and produces gamma rays (two at 180 degrees apart) when the positron interacts with an electron. Gamma rays are detected with a scintillation counter and can be mapped back onto the patient to determine where in the body the signal originated.

FDG is a commonly used radionuclide that is taken up by metabolically active tissue, and thus can be used to localize metastases or determine sites of brain activity.
Pittsburgh Compound B (PiB)

PiB-PET signal is 1.5- to 2-fold increased in AD frontal, parietal, temporal & occipital cortex, as well as striatum.

PIB levels are similar between Alzheimer’s disease and control patients in areas not affected by amyloid.

There is an inverse correlation between PIB retention and cerebral glucose metabolism (FDG-PET).

Klunk et al, 2004
PiB Identifies Alzheimer’s disease and MCI

PiB has been widely validated in identifying Alzheimer’s disease. It can also be used to detect Mild Cognitive Impairment (MCI), which is a precursor condition to Alzheimer’s disease. PiB signal elevation is detected before a decrease in FDG.

PET, axial plane

Lowe et al, 2009
Use of PiB To Assess Clinical Trials

The phase II trial of bapineuzumab, an anti-amyloid monoclonal antibody, used PiB-PET to image a subset of enrolled patients. This radiologic marker provides a quantitative means of assessing amyloid clearance.
Several complimentary molecular imaging markers have been identified that label other aspects of neurodegenerative disease pathology.
The molecule FDDNP binds to amyloid plaques and tangles (another pathologic feature of Alzheimer’s) \textit{in vivo}. FDDNP-PET is better at differentiating normal, MCI and Alzheimer’s disease brains than FDG-PET.
Mononuclear phagocyte lineage cells, including brain microglia, expresses **Peripheral Benzodiazepine Binding Sites**, which are bound by carbon-11-labeled PK11195. Greater PET signal is seen in Alzheimer’s disease than MCI due to extensive gliosis associated with neurodegeneration. Little background PET signal is seen in normal age-matched controls.
Dementia Imaging Conclusions

1) PiB and similar imaging agents use disease-specific pathologic principles to non-invasively visualizing dementia. They are sufficiently sensitive to detect dementia precursor states. Amyloid burden detected by imaging correlates well with post-mortem analysis.

2) Radiologic markers of dementia will be useful for early detection, accurate diagnosis, clinical trial assessment and therapeutic intervention.

3) Amyloid imaging is not specific for Alzheimer’s disease: other forms of dementia with amyloid accumulation also increase PiB signal (e.g. Dementia with Lewy Bodies). Lower PiB uptake has been demonstrated in Parkinson’s disease & Frontotemporal dementia, making PiB useful in ruling out these diagnoses.

4) Carbon-11 has a short half life (20 min), making its use inconvenient. Flourine-18 has a longer half life (110 min), but may be challenging to incorporate into a PiB-like molecule.
References

Gillian Lieberman, MD
Rafael Rojas, MD
James Knutson, MD
Maria Levantakis
BIDMC Radiology Department