

# Molecular Imaging Rounds

*A Newsletter for Referring Physicians*



## Neuroimaging for Dementia and Alzheimer's Disease

- **CT or MRI are appropriate under most circumstances at the time of initial dementia assessment to identify rare pathologies such as neoplasms or subdural hematomas**
- **When specific clinical criteria are met, FDG-PET can be utilized to distinguish between Alzheimer's and Pick's (fronto-temporal) disease**
- **Molecular imaging examinations that detect specific biological characteristics of Alzheimer's disease, currently used as research tools, will become clinically available in the future for early detection of disease**

There are an estimated 4.5 million people in United States with Alzheimer's disease (AD) at this time, accounting for approximately 60 to 70% of all cases of dementia in the elderly. As the baby-boomer population ages, it is expected that the number of Alzheimer's patients will grow dramatically, increasing the burden on both the public health care system as well as caregivers of these patients. While there are medications that may delay progression of symptoms, treatments available at this time for AD are not effective at slowing disease progression. Promising disease-modifying therapies for AD however are currently in large scale clinical trials and it is likely that some will become available within the next few years.

The definitive diagnosis of AD can only be made by the detection of amyloid plaques and neurofibrillary tangles at autopsy. A clinical diagnosis based on the history, physical examination, neuropsychological evaluation, and laboratory tests is usually accurate in established cases, but is more challenging in earlier, milder forms of the disease. The role of neuroimaging at present is primarily to identify potentially treatable underlying conditions that arise in patients with unusual presenting symptoms. While AD is by far the most common form of dementia (Table 1), other etiologies must be considered because prognosis and management strategies will differ. Neuroimaging is often useful for this purpose, for example, in differentiating vascular and fronto-temporal dementias from AD. The role of neuroimaging in the next few years will likely also include the direct identification of early amyloid AD pathology with positron emission tomography (PET).

### MRI and CT

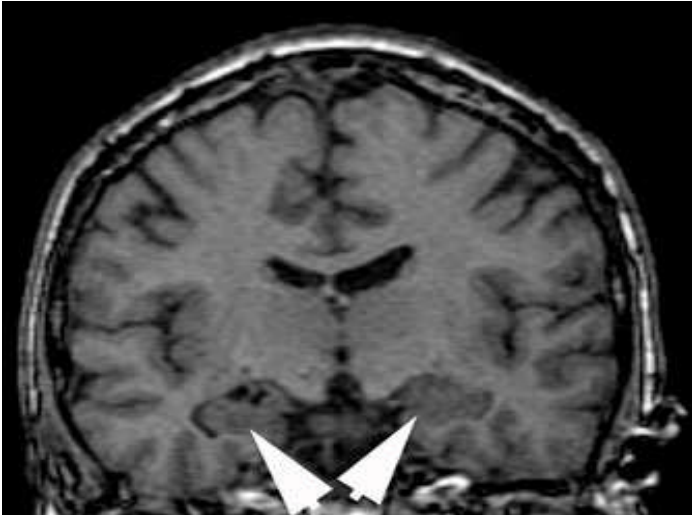
By the time AD symptoms are clinically established, structural brain shrinkage in excess of normal aging is often evident and readily detectable with either CT or MRI. AD causes atrophy of the entire brain,

**Table 1. Relative frequencies of causes of dementia in elderly patients**

Alzheimer's Disease	60-70%
Vascular dementia	20%
Mixed etiology	6%
Fronto-temporal dementia	5-10%
Dementia with Lewy bodies	25%
Normal pressure hydrocephalus	1%
Depression	1%
Tumor	1%

Note: Patients may have more than one cause of dementia

although some regions such as the hippocampus are specifically affected by AD and can be assessed with quantitative volumetric methods, usually applied to MRI (Figure 1). Up to 5% of patients presenting for initial evaluation for dementia harbor a clinically significant structural lesion that is not identified by history or examination. Most commonly, these lesions are infarcts but occasionally neuroimaging can reveal a tumor or subdural hematoma requiring surgical evaluation. CT is usually adequate as an initial examination to look for these lesions. Dementia on the basis of cerebrovascular disease may occur alone or in combination with AD ("mixed" dementia) and is associated with white matter abnormalities that are more evident with MRI. Vascular dementia remains a clinical diagnosis. Minimal changes on MRI, including white matter abnormality and mild brain atrophy, are usually age-related and may provoke unnecessary concern. Normal-pressure hydrocephalus is an uncommon condition whose clinical symptoms include ataxia, incontinence, and dementia; imaging typically shows ventricular enlargement.



**Figure 1.** Coronal MR image of the brain, showing hippocampi (arrows). Serial imaging, which is not used in clinical practice, is necessary to demonstrate selective shrinkage of the hippocampus that is characteristic of AD.

## FDG-PET Imaging

FDG-PET is useful for distinguishing between Alzheimer's and fronto-temporal (Pick's) dementias and is approved by Medicare for this purpose. FDG-PET images show the regional distribution of the rate of glucose metabolism. Normal neurons have a very high metabolic rate and therefore FDG uptake is high in brains of healthy subjects, especially in the cortex. In contrast, FDG uptake in AD is greatly diminished, especially in the temporal and parietal regions of the brain. The characteristic pattern of FDG uptake seen in Alzheimer's patients is very different from that seen in other forms of dementia, such as fronto-temporal dementia (Figure 2), allowing these diseases to be differentiated.

Before a FDG-PET study for dementia is ordered, a referral form should be completed that documents the indication and potential benefit of FDG-PET for clinical management of the patient (Table 2).

### Table 2. Medicare Requirements for Ordering FDG-PET for Dementia Patients

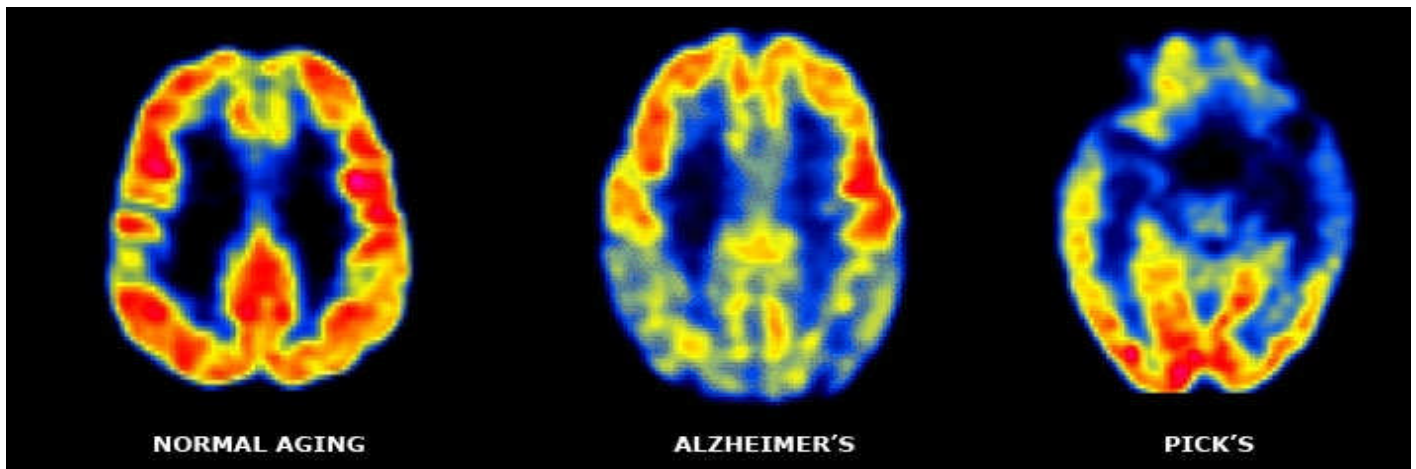
- At least 6 months of progressive cognitive decline
- Cause of symptoms remains uncertain
- Completed comprehensive neurological examination by a physician experienced in diagnosis and assessment of dementia
- Meet diagnostic criteria for Alzheimer's or fronto-temporal dementia
- No prior brain SPECT or FDG PET for same indication

## Quantitative Analysis

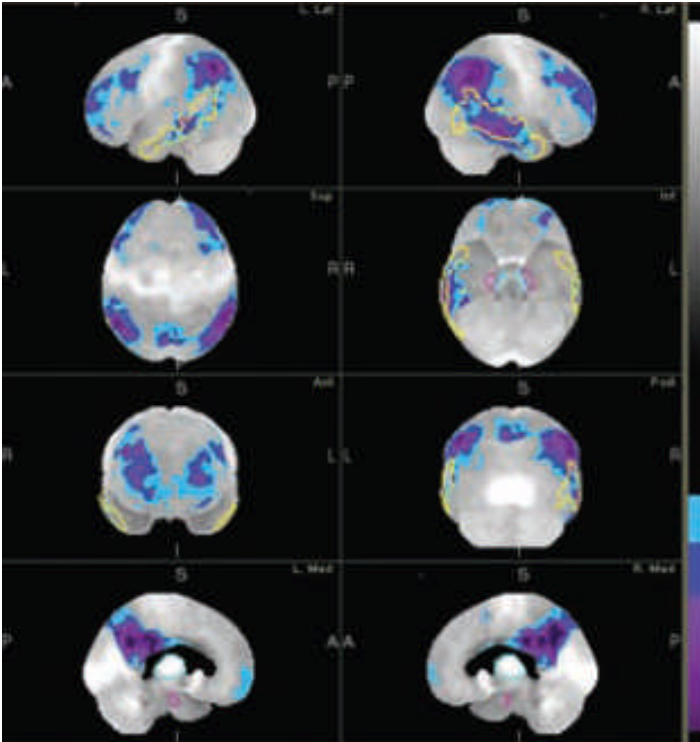
As an aid in the evaluation of FDG-PET studies of patients with dementia, several automated quantitative and statistical analysis tools have been developed. 3-dimensional stereotaxic surface projection (3D SSP) analysis is one such tool, which generates a comprehensive image presentation with quantitative indices. The tool allows an individual's study to be compared with age-range-matched normal controls by calculating Z-scores on a voxel by voxel basis and displaying the results in a 3-dimensional brain surface image (Figure 3). These tools enhance the overall sensitivity and value of serial examinations.

## Future Imaging Techniques for Dementia

Proton magnetic resonance spectroscopic imaging (MRS) can be performed as an add-on examination after conventional MRI. Proton MRS imaging assesses several characteristic hydrogen-containing biochemicals in an array of voxels, each about 2-7 cm<sup>3</sup>, which are displayed as a spectrum for each voxel of tissue. One of the principal peaks in the spectrum of a healthy brain is that of the neuronal marker, n-acetyl aspartate (NAA), while other major peaks include choline, creatinine, and myo-inositol. Even before the development of overt dementia due to AD, there is a decrease in the ratio of NAA: creatinine in the temporal lobe, which is not seen in patients whose memory loss and cognitive declines are attributed to other causes of dementia.



**Figure 2.** FDG PET images showing a pattern of metabolism in a normal elderly individual and patterns of decreased metabolic activity that are characteristic for Alzheimer's and Pick's disease. Red: high FDG uptake, Blue: low FDG uptake



**Figure 3.** 3D SSP images showing areas of low FDG uptake in an Alzheimer's patient. Blue-Purple areas represent greater than 1.65 standard deviations below the normal age-matched database.

Several highly specific PET imaging agents have been developed which bind to the characteristic  $\beta$ -amyloid plaque found in AD. Currently, the most sensitive and specific of these, known as Pittsburgh Compound B (PIB), rapidly crosses the blood brain barrier and is retained by  $\beta$ -amyloid fibrils, but not in normal brain tissue. In Alzheimer's patients, high contrast images are possible showing retention of PIB in areas where  $\beta$ -amyloid is characteristically found, such as the parietal and frontal cortices. In contrast, patients with fronto-temporal dementia have normal-appearing PIB images.

Interestingly, PIB binding is seen in approximately 20% of apparently normal older subjects, and whether this is an indication of antecedent AD is a topic of intense investigation. PIB-PET also has applications in current drug development as it may be used to demonstrate whether drugs designed to act on  $\beta$ -amyloid are able to reduce or stabilize the burden of  $\beta$ -amyloid plaque.

At this time, both proton MRS and PIB-PET are research tools. However, with the recent dramatic advances in understanding the biology of Alzheimer's disease and the expectation that drugs will become available to treat it, these neuroimaging tools will likely be brought into the clinical mainstream for early diagnosis and intervention.

## Scheduling

FDG-PET may be ordered by telephone at 520.321.4057 in Tucson or 928.314.4800 in Yuma after the completion of a referral form.

## For Further Information

For further questions, please contact:

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