

July 2012

Conference Insights:



A Continuing Medical Education Series

Molecular Imaging in the Differential Diagnosis of Alzheimer's Disease and Other Dementias*

* This program's educational content is based, in part, on various abstracts, posters, presentations, and interviews from the Society of Nuclear Medicine and Molecular Imaging (SNMMI) 2012 Annual Meeting, which took place June 9–13 in Miami, Florida. This publication was prepared under the design and production supervision of Dothen Healthcare Press. It is not sanctioned by the SNMMI, nor is it an official publication of the Annual Meeting of the SNMMI. The Society of Nuclear Medicine officially changed its name to the Society of Nuclear Medicine and Molecular Imaging on June 11, 2012.

Conference Insights:



This activity is supported by an educational grant from Lilly USA, LLC. For further information concerning Lilly grant funding visit www.lillygrantoffice.com

A Continuing Medical Education Series

IN THIS ISSUE: MOLECULAR IMAGING IN THE DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS*

SUMMARY HIGHLIGHTS

Summary highlights from presentations addressing molecular imaging of neurodegenerative disorders at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) 2012 Annual Meeting (June 9–13; Miami, Florida) and 2 case studies provided by Adam Fleisher, MD, MAS, Course Director:

Best practices for the use of ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and amyloid-PET in the evaluation of cognitive decline and dementia are not yet clear. An SNMMI and Alzheimer's Association Amyloid Imaging Task Force is developing guidelines for the use of amyloid-PET.

FDG-PET is not approved by FDA for the dementia indication, but is reimbursed by Centers for Medicare & Medicaid Services (CMS) for the differential diagnosis of frontotemporal dementia (FTD) and Alzheimer's disease (AD).

Florbetapir is the only FDA-approved amyloid-PET radiopharmaceutical. Three additional amyloid-PET agents are in phase 2 and 3 clinical trials.

A positive amyloid-PET scan does not diagnose AD, and is necessary but not sufficient for a diagnosis of AD. A negative amyloid-PET scan indicates that cognitive impairment is very unlikely to be caused by AD.

Based on research findings, FDG-PET imaging is used clinically to determine relevant areas of cortical glucose hypometabolism in the differential diagnosis of patients with dementia of unknown cause, AD vs FTD, and AD vs dementia with Lewy bodies, among others. However, more data are needed to determine the optimal role of FDG-PET vs amyloid-PET.

Current data suggest potential clinical roles for amyloid-PET to determine the presence or absence of amyloid pathology in the differential diagnosis of AD vs FTD, mild cognitive impairment, early onset dementia, dementia with atypical or focal features, and when AD is suspected but alternative causes for cognitive decline are present, among others.

Clinical evaluation of a cognitive syndrome by a clinician experienced in dementia is recommended before proceeding to a molecular imaging test.

Although no disease-modifying treatment is currently available, the correct diagnosis of a patient's cognitive deficit or dementia has therapeutic and management implications for current practice.

PET biomarkers can improve the purity of subject populations in clinical trials of potential disease-modifying therapeutics for dementia and might eventually serve as surrogate endpoints in clinical trials, reducing the size (number of subjects) and duration of these trials.

OVERLAPPING PATHOLOGIES AND DEMENTIA SYNDROMES

Neurodegenerative syndromes are associated with the deposition of amyloid-beta peptide, and tau and alpha-synuclein proteins. A patient's specific syndrome is defined by observation of 1 or more of these pathologic deposits. Figure 1 links neurodegenerative syndromes to their associated peptide/protein deposits.

Figure 1: Amyloid-Beta, Tau, and Alpha-Synuclein Deposition in Neurodegenerative Syndromes

Neurodegenerative syndrome	Amyloid-beta	Tau	Alpha-synuclein
Amyloid angiopathy	X		
Alzheimer's disease (AD)	X	X	
Frontotemporal dementias		X	
Progressive supranuclear palsy		X	
Cortical-basal degeneration		X	
Parkinson's dementia			X
Dementia with Lewy bodies	+/-		X
Lewy body variant of AD	X	X	X

Derived from: Frey KA. Molecular imaging of neurodegenerative disease. Presented at: SNMMI 2012 Annual Meeting; June 9–13, 2012; Miami FL.

Two hallmark neuropathological lesions are required for a definitive diagnosis of Alzheimer's disease (AD): amyloid-beta, an extracellular peptide deposit, and tau protein, which forms intracellular neurofibrillary tangles. Amyloid angiopathy is associated with amyloid-beta deposition alone (in blood vessels). Tau deposition alone occurs in frontotemporal dementias, progressive supranuclear palsy, and cortical-basal degeneration. Parkinson's disease dementia is associated with alpha-synuclein protein deposition alone. Dementia with Lewy bodies is always characterized by alpha-synuclein deposition, but many brains also demonstrate the cortical amyloid-beta deposits characteristic of AD. In the Lewy body variant of AD, all 3 degenerative processes and deposition of all 3 pathologic compounds are observed.

It is not until autopsy, when characteristic lesions of specific dementia syndromes can be identified under the microscope, that definitive diagnoses can be made. Brain biopsy is not performed in the living patient because no effective disease-modifying treatment is currently available.

Also in This Issue:

4 Amyloid Imaging: Development and Research Highlights

5 Current Status of Molecular Imaging Modalities in the Clinical Assessment of Cognitive Decline and Dementia

6 Clinical Case Studies

2 Molecular Imaging of Dementia Coming of Age

3 FDG-PET In AD and Other Dementias

5 Why Diagnose Cognitive Decline and Dementia with Molecular Imaging Modalities?

3 Challenges of Dementia Diagnosis

5 ¹⁸F Amyloid Imaging Agents

6 References & Further Reading

Conference Insights: Molecular Imaging in the Differential Diagnosis of Alzheimer's Disease and Other Dementias

CME ACCREDITATION

Release Date: 7/19/2012 • Expiration Date: 7/19/2013

Course Director: Adam S. Fleisher, MD, MAS

Geriatric Neurologist, Dementia Specialist
Director, Brain Imaging
Banner Alzheimer's Institute
Phoenix, Arizona

Medical Director, Alzheimer's Disease Cooperative Study
Associate Professor, Department of Neurosciences
University of California, San Diego

Medical Writer: Timothy Tankosic, MD

Managing Director, Aqua Partners, LLC
Consultant, Neuroscience-based Therapeutics and Diagnostics

Planners: Bill Jacobs, PhD • Erika Gettings

Disclosure of Conflicts of Interest: All faculty members participating in continuing medical education programs sponsored by MedEDirect are expected to disclose any real or perceived conflicts of interest related to the content of the activity.

Dr Fleisher reports that he serves as a consultant for Siemens, Avid, Eli Lilly, and Merck & Co.

Dr Tankosic, Bill Jacobs, and Erika Gettings have nothing to disclose.

Needs Statement/Overview

Age-related decline in multiple cognitive domains is common, and for some may be attributed to the onset and/or progression of dementia. Alzheimer's disease (AD) is a common neurodegenerative form of dementia with hallmark clinical signs and symptoms that include memory impairment, irreversible cognitive decline, and behavioral and language changes. Based on an aging population, the disease burden trajectory suggests that by 2050, more than 13.5 million individuals in the US will be affected by AD. Examination of AD patient brain tissue after death reveals distinct neuropathologic features, in particular the presence of senile plaques and neurofibrillary tangles that contain β -amyloid peptides (A β) and highly phosphorylated tau proteins. Currently, the clinical diagnosis of AD is deduced from a patient's history and memory testing, but is only known definitively through postmortem histopathologic examination of the brain for A β and tau protein plaque deposits. However, recent advances in neuroimaging and the development of metabolic, receptor, and molecular probes for positron emission tomography (PET) scan applications are providing valuable insights into morphologic and biologic changes associated with earlier stages of dementia disease processes. Appropriate clinical use of these probes for patients with minimal changes or ambiguous clinical diagnosis are providing important insights into the early identification of patients with specific dementia disorders. Understanding the utility and limitations of these new aids to diagnosis offers an important advance in the identification and management of patients with and without dementia.

Physician Accreditation

Accreditation Statement: MedEDirect is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation: MedEDirect designates this educational activity for a maximum of 1.0 hour *AMA PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Learning Objectives

At the end of this activity, participants should be able to:

1. Understand the development process for novel neuroimaging agents.
2. Gain familiarity with new technological advances in neuroimaging.
3. Describe new methods, such as amyloid-PET imaging, in dementia workup.
4. Identify the various pathological processes that take place during the onset and course of Alzheimer's disease, and how these can be visualized and quantified using molecular imaging.
5. Demonstrate clinical competence in the use of amyloid neuroimaging.
6. Apply knowledge of various brain imaging modalities, such as amyloid-PET imaging, for dementia workup.

Target Audience

This educational program is intended for neurologists involved with the detection and treatment of Alzheimer's disease.

Estimated Time of Completion

This activity should take approximately 1.0 hour to complete.

Method of Participation

There are no fees for participating in and receiving credit for this activity. The participant should complete the multiple-choice pre-test, read the objectives and meeting report, and complete the multiple-choice post-test and evaluation. Participants may then claim credit for participation.



Dear Reader:

Although a definitive diagnosis of Alzheimer's disease (AD) is obtained only at autopsy, we can now evaluate patients in the clinic using accurate biomarkers to identify key underlying AD pathology. The risk factor gene, apolipoproteinE epsilon 4, cerebrospinal fluid levels of amyloid and tau proteins, and MRI and ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scans have been available to most clinicians. And earlier this year, amyloid-PET imaging became available for clinical use in the United States.

We do not yet fully understand which combinations of biomarkers will best predict clinical outcomes and at which disease stages each will be most valuable. Ongoing longitudinal studies, however, give promise for better understanding and development of best-practice guidelines for the use of novel AD biomarkers in the diagnostic workup.

Research implications of new imaging techniques are great. They have provided strong evidence that AD pathology is present in patients long before clinical syndromes become apparent, and they have become critical research tools for the development of preventative therapies and treatments for prodromal AD.

In clinical practice, FDG-PET plays a role in the evaluation of dementia of unknown etiology. Amyloid-PET is currently indicated only for the evaluation of cortical amyloidosis as part of a diagnostic workup in patients with discernible cognitive symptoms. However, amyloid imaging might eventually play an important role in predicting which cognitively normal adults will go on to develop AD.

This year's Society of Nuclear Medicine and Molecular Imaging conference (June 9–13, 2012) highlighted the increasing role of PET imaging in the evaluation of the patient with cognitive decline and dementia. These are exciting times, as new PET techniques help transform the basis of clinical diagnosis from symptom phenomenology alone to one that includes evidence of underlying pathologies.

Adam S. Fleisher, MD, MAS
Course Director

Director of Brain Imaging, Banner Alzheimer's Institute
Medical Director, Alzheimer's Disease Cooperative Study
Associate Professor, Department of Neurosciences
University of California, San Diego

MOLECULAR IMAGING OF DEMENTIA COMING OF AGE

The use of molecular imaging technologies for assessment of cognitive decline and dementia has advanced from research promise to clinical reality. In April 2012, FDA approved ¹⁸F-florbetapir (Amyvid[™]; Eli Lilly & Co., Indianapolis, Indiana), a radiopharmaceutical used in positron emission tomography (PET) for brain imaging of amyloid-beta plaques in patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline. In January 2011, Ioflupane ¹²³I injection (DaTscan[™]; GE Healthcare, Waukesha, Wisconsin) was approved for use with single-photon emission computed tomography for detection of dopamine transporters in the brains of adult patients with suspected Parkinsonian syndromes. In addition to these 2 new radiotracers and ¹⁸F-fluorodeoxyglucose (FDG-PET), which had already been in clinical use, 3 new developmental amyloid-PET agents may become available in the next few years.

Instructions for Claiming Credit Online

1. Go to www.mededirect.org
2. Click on the **Educational Offerings** tab.
3. Click on the **"Molecular Imaging in the Differential Diagnosis of Alzheimer's Disease and Other Dementias"** icon.
4. Follow the prompts on the screen to download the monograph in PDF format, or go directly to the post-test and evaluation.
5. You will be able to download your CME certificate on completion of the post-test and evaluation.

CHALLENGES OF DEMENTIA DIAGNOSIS

In his plenary address, *Molecular Imaging of Neurodegenerative Disease*, Kirk A. Frey, MD, PhD, of the University of Michigan, at this year's SNMMI meeting summarized the clinical need for new radiotracers to improve diagnosis of dementia over the current standard. The arrival in the clinic of new agents is timely. More patients will need dementia diagnostic services because prevalence and associated costs are increasing rapidly as populations age in developed countries. Dementia often presents a difficult diagnostic challenge because clinical signs and symptoms, particularly early in the neurodegenerative process, may be consistent with more than one syndrome. Routine clinical diagnostic accuracy is only about 60% to 80%. Although diagnoses improve as patients are followed over time, diagnoses remain uncertain in more than 20% of cases, even in the best specialty dementia clinics. Criteria have been established for clinical dementia diagnosis in Alzheimer's disease (AD), behavioral variant frontotemporal dementia, and dementia with Lewy bodies.¹⁻³ Figure 2 summarizes dementia demographics and costs.⁴

Figure 2: AD and Other Dementia Demographics and Costs (US)

AD prevalence, 2011	5.4 million cases
AD cause of death, 2008	82,435*
All dementia prevalence, age ≥71 years	13.9%
AD percentage of all dementia	60% to 80%
Non-AD dementia types	<ul style="list-style-type: none"> • Vascular dementia • Dementia with Lewy bodies • Mixed dementia • Parkinson's dementia • Frontotemporal dementias • Creutzfeldt-Jakob disease • Normal pressure hydrocephalus
Cost of care,** AD and other dementias, 2012	\$200 billion
Value of unpaid care, AD and other dementias, 2011	>\$210 billion
Projected 2025 AD prevalence, age ≥65 years	6.7 million
Projected 2050 AD prevalence, age ≥65 years	11 to 16 million***

* Deaths attributed to AD increased by 66% from 2000 to 2008, but this increase is likely underestimated because acute conditions are often listed as the primary cause of death.
 ** Includes healthcare, long-term care, and hospice.
 *** Assumes no treatment becomes available to prevent, slow, or halt AD.
 Source: Alzheimer's Association, Thies W, Bleiler L. 2012 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2012;8(2):131-168.

FDG-PET IN AD AND OTHER DEMENTIAS

Satoshi Minoshima, MD, PhD, of the University of Washington in Seattle, at the recent SNMMI Annual Meeting reviewed the use of ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging in Alzheimer's disease (AD) and other dementias. Initial studies in the 1980s for imaging brains of patients with AD showed promise for differential diagnosis of dementia. Investigation intensified in the mid-1990s, yielding significant FDG-PET correlations (areas of glucose hypometabolism) with brain vulnerabilities in AD and other dementias.

A review of literature since 2000 supports the role of FDG-PET as an adjunct to other diagnostic information in the assessment of patients with symptoms of dementia. The review includes autopsy confirmation, wide-diagnostic-spectrum recruitment in primary care settings, historical and prospective cohort studies, and multicenter data analyses. The recently revised diagnostic criteria for AD recognize the importance of biomarker evidence in disease definition.⁵

FDG-PET may be useful for differential diagnosis when the cause of dementia is not clear, such as distinguishing between AD and frontotemporal dementias (FTD), because key FDG-PET findings are "opposite." Figure 3 summarizes FDG-PET findings in selected dementias. FDG-PET findings in AD from dementia with Lewy bodies (DLB) are identical, except in the visual cortex. In DLB the visual cortex is typically affected; in AD the visual cortex usually is not affected until end stages of the clinical disease. FDG-PET is approved for Medicare reimbursement specifically for the differential diagnosis of FTD and AD, but not FDA-approved for the general dementia indication.

According to Dr Minoshima, because FDG-PET measures glucose uptake at synapses, rather than at neuronal cell bodies, it can identify the synaptic changes that occur years before onset of AD symptoms. A longitudinal assessment of cerebrospinal fluid (tau, amyloid-beta) and FDG-PET biomarkers is needed to determine whether the observed changes predict cognitive impairment and incipient AD.⁶

Figure 3: FDG-PET Findings in Dementias

Dementia	Cortical glucose hypometabolism	Preserved glucose metabolism	Diagnostic notes
Alzheimer's disease (AD)	<ul style="list-style-type: none"> • Posterior cingulate/precuneus cortex • Posterior temporoparietal association cortex 	<ul style="list-style-type: none"> • Primary somatomotor cortex • Primary visual cortex (occipital cortex) • Basal ganglia • Thalamus • Posterior fossa: brainstem, cerebellum 	<ul style="list-style-type: none"> • Hypometabolism of frontal cortex in advanced disease • Differential diagnosis (DDx) vs FTD: key findings opposite • DDx vs DLB: visual cortex not typically affected in AD
Frontotemporal dementias (FTD)	<ul style="list-style-type: none"> • Frontal lobes • Anterior cingulate • Anterior temporal cortex 	<ul style="list-style-type: none"> • Posterior cingulate relatively preserved 	<ul style="list-style-type: none"> • DDx vs AD: key findings opposite
Dementia with Lewy bodies (DLB)	<ul style="list-style-type: none"> • Same as AD 	<ul style="list-style-type: none"> • Same as AD 	<ul style="list-style-type: none"> • DDx vs AD: visual cortex typically affected in DLB

Source: Presentations at the SNMMI 2012 Annual Meeting.

AMYLOID IMAGING: DEVELOPMENT AND RESEARCH HIGHLIGHTS

Recent developments in amyloid-positron emission tomography (PET) imaging dominated this year's SNMMI conference research presentations related to dementia and cognitive decline.

Chester A. Mathis, PhD, reviewed his work with William Klunk, MD, PhD, and others at the University of Pittsburgh, in the development of the first amyloid-PET agent, Pittsburgh compound B (PiB). Their starting point in 1993 was Congo red, the stain used by neuropathologists to identify amyloid-beta plaques at autopsy. Congo red is not suitable an amyloid-PET radioligand because it is charged and hydrophilic and therefore does not cross the blood-brain barrier (BBB). Mathis and Klunk developed hundreds of derivatives of Congo red and other compounds without success. Peptides and proteins (eg, antibodies) were rejected because of their very slow BBB uptake. Finally, they chose the dye Thioflavin-T, which required removal of only 1 charged group to achieve neutrality, and they developed a series of benzothiazole anilines (6-Me-BTA). Refinement of this approach led to the development of 6-OH-BTA-1 (PiB).

PiB demonstrated neutral lipophilic character (crosses BBB), high affinity for amyloid-beta (100-fold > parent compound), rapid non-specific clearance ($t_{1/2}$ = 6 minutes), and no radiolabeled metabolites in the brains of humans. In a stroke of remarkable luck, PiB was found to bind specifically to amyloid-beta (1-40, 1-42), unlike the parent compound, which is a pan-amyloid binding agent that binds also to tau, prions, alpha-synuclein, huntingtin, and other forms of amyloid. The first clinical study with PiB, performed in 2002 in Uppsala, Sweden, demonstrated the expected amyloid plaque distribution in the brain of an Alzheimer's subject.

Clinical research with PiB forms the basis for most of our understanding of the relationship between in vivo amyloid-beta deposition and Alzheimer's disease (AD) and AD-related cognitive decline. Amyloid-PET research highlights include:

In AD, brain amyloid burden increases rapidly to near-peak levels before any symptoms of AD occur, then continues to accumulate at a very slow rate.

This surprising discovery led to the development of AD models of:

- 2 stages of AD pathophysiology: amyloid-beta dependent and amyloid-beta independent stages⁷; see Figure 4
- 3 clinical phases of AD: preclinical phase (no symptoms), prodromal/mild cognitive impairment (MCI) phase (cognitive symptoms only), and the Alzheimer's dementia phase (frank dementia)
- Multiple AD biomarkers appear during different phases of the Alzheimer's pathological cascade⁹

These findings, along with ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and volumetric MRI (vMRI) results, suggest that amyloid imaging may be most informative in the early stages of AD. Note that in Figure 4, the amyloid burden curve flattens after the early, rapid deposition phase, indicating that additional amyloid deposition is not required for progression to dementia and that amyloid-PET findings in individual patients will change only incrementally over time. Earlier studies support the notion that neurofibrillary

tangles and neuron numbers, more than amyloid load, predict cognitive status in AD. FDG-PET and vMRI may be more informative for following patients across all stages of AD.

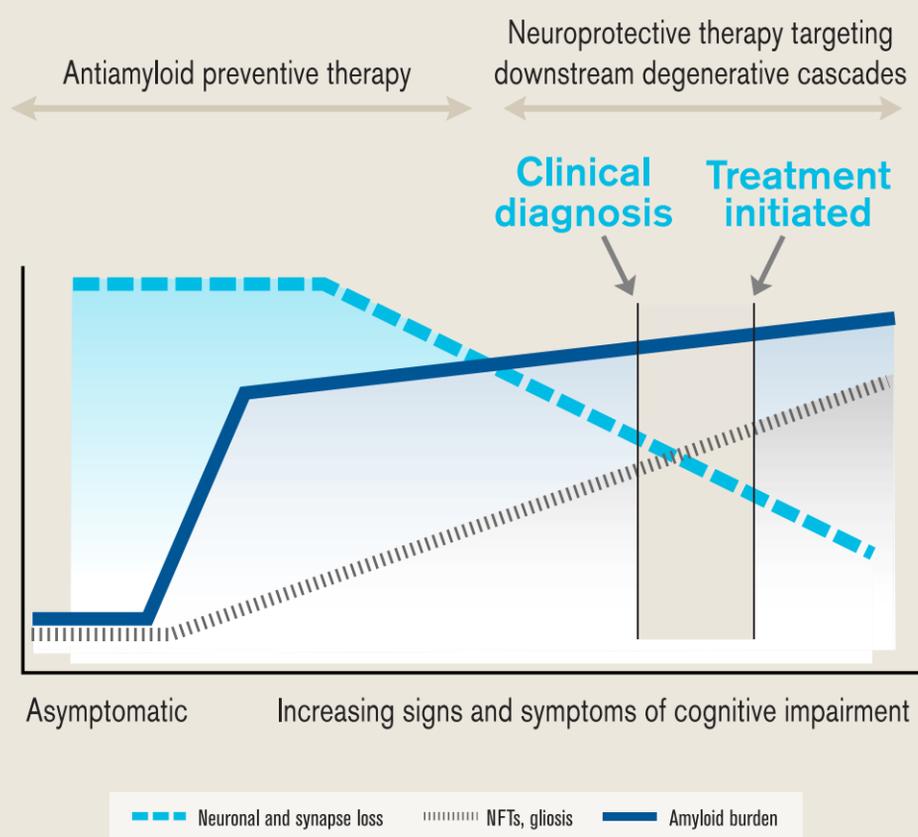
Some elderly control (cognitively normal) subjects have positive amyloid scans.

Various studies¹⁰, now totaling about 1000 normal subjects, show that about 33% of cognitively normal controls demonstrate positive amyloid scans. Postmortem studies have confirmed this finding and shown increased amyloid-beta plaques (positive amyloid scan) in the cognitively normal elderly. How is this reconciled? If these subjects had lived longer, would they have developed cognitive decline and AD? Currently, large, 15-year-long, longitudinal studies are underway to determine whether normal subjects with positive amyloid scans will develop AD.

In studies of MCI, about two-thirds of MCI subjects demonstrate AD-like amyloid scans (ie, high plaque loads), and about one-third show almost no amyloid.

This finding was explained by available epidemiological studies of MCI. MCI is a catchall category from which about two-thirds of patients go on, over time, to develop AD, and one-third do not. Since the initial report, many other groups¹¹ have reported amyloid-positive scans in MCI subjects. Dr Mathis presented aggregated data from four 2-year prospective studies that included amyloid status in MCI subjects (n=115): one-third were amyloid-negative and two-thirds were amyloid-positive. At the end of the 2 years, 62% of the amyloid-positive MCI subjects had gone on to develop probable AD; and only 2/39 of the amyloid-negative MCI subjects had developed probable AD. Postmortem examination will reveal whether the 2 amyloid-negative MCI subjects were misdiagnosed with AD 2 years later.

Figure 4: Therapeutic Implications of a 2-phase Pathophysiology of Alzheimer's Disease



Data from a cross-sectional neuropathological study modeling the accumulation of plaques, tangles, neuronal loss, and synaptic and glial alterations, compared with clinical severity of illness (modified from Ingelsson, et al).⁸ A similar pattern is evident from analysis of MRI and amyloid-PET scans in vivo, as suggested by the Alzheimer's Disease Neuroimaging Initiative.

NFTs, neurofibrillary tangles.

Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. *Arch Neurol.* 2011;68(8):1062-1064.

Copyright © 2011 American Medical Association. All rights reserved.

¹⁸F AMYLOID IMAGING AGENTS

The short, 20-minute half-life of ¹¹C-based Pittsburgh compound B (PiB) limits its use to positron emission tomography (PET) centers with the capability of producing their own radiotracers. The short half-life of PiB was the principal driver for the development of ¹⁸F amyloid imaging agents. The new agents have significantly longer half-lives (eg, florbetapir has a half-life of about 110 minutes), providing much greater reach into the more than 2000 PET scanners in the US. PiB is also not a perfect agent because of non-specific white matter retention. Improving tracer

brain pathology, with high degrees of sensitivity and specificity, in autopsy studies.¹² Flutemetamol and florbetaben, both in phase 3, have also demonstrated positive results in autopsy studies.

Amyloid-PET studies of mild cognitive impairment (MCI) and normal aging are beginning to emerge. One study introduces threshold levels of florbetapir positivity associated with an intermediate-to-high likelihood of pathologic Alzheimer's disease (AD) or having any identifiable cortical amyloid level above

In clinical practice, it is recommended that imaging physicians complete an Amyvid training course either online or at a live training session before clinical use of florbetapir-PET. The Amyvid training program was launched in June. Amyvid is currently available to imaging centers in areas surrounding 16 manufacturing sites throughout the US. More manufacturing centers are expected to open by the end of year in order to increase access to this biomarker.

Flutemetamol has a structure that differs by 1 atom (C) from that of florbetapir (N). Data presented at the conference showed strong correlation of flutemetamol with amyloid-beta deposition in subjects with AD. In April, it was reported that two phase 3 trials met their endpoints and that an FDA submission was imminent.

Florbetaben. Christopher Rowe, MD, FRACP, of Austin Health (Melbourne, Australia), presented results of a 2-year longitudinal study of florbetaben imaging of amyloid-beta deposition in 45 subjects with MCI. At 2 years, the 75% of subjects who had demonstrated high uptake of florbetaben progressed to AD, representing a nearly 11-fold increase over the low uptake group ($P < 0.0001$). An earlier study by Rowe and colleagues found that florbetaben had high sensitivity for AD, clearly distinguished patients with frontotemporal dementia (FTD) from AD, and also provided results comparable to those reported with PiB in a variety of neurodegenerative diseases.

Osama Sabri, MD, of the University of Leipzig, reported high levels of sensitivity (100%) and specificity (91.7%) in a 31-subject (25 demented, 6 controls) autopsy study with florbetaben.

AZD4694 is similar in structure to PiB. Dr Rowe and colleagues reported results of a study in 25 control, 10 MCI, 7 AD, and 3 FTD subjects. AZD4694 followed the known distribution of amyloid-beta in the brain, was highly correlated with PiB, and showed low non-specific retention in white matter (not $> \text{PiB}$).

Figure 5: ¹⁸F Amyloid Imaging Agents

Agent	Company	US Status
Florbetapir	Eli Lilly & Co. (Indianapolis, Indiana)	Approved
Flutemetamol	GE Healthcare (Waukesha, Wisconsin)	Phase 3
Florbetaben	Piramal Healthcare (Mumbai, India)	Phase 3
AZD4694	Navidea Biopharmaceuticals (Dublin, Ohio)	Phase 2

Sources:

Petra R. Flutemetamol for Alzheimer's - phase 3 results released. Medical News Today. <http://www.medicalnewstoday.com/articles/244103.php>. Published April 13, 2012. Accessed July 13, 2012.

Phase III study of florbetaben (BAY94-9172) PET imaging for detection/exclusion of cerebral β -amyloid compared to histopathology. ClinicalTrials.gov. <http://www.clinicaltrials.gov/ct2/show/NCT01020838>. Updated on May 24, 2012. Accessed July 13, 2012.

specificity and signal-to-noise ratio is a goal of new radiotracer development. Figure 5 lists ¹⁸F amyloid imaging agents. Clear differentiation of these agents by clinical performance characteristics (eg, ease of reading/signal-to-noise ratio) awaits more data.

Florbetapir (Amyvid™; Eli Lilly & Co., Indianapolis, Indiana) is the only FDA-approved amyloid-PET agent. FDA required proof in phase 3 clinical trials that florbetapir was depicting amyloid deposition (rather than an unknown phenomenon), which was confirmed by matching individual florbetapir scan results with

that seen in low-risk, young controls.¹³ Michael Devous, PhD, of the University of Texas, reported at this year's SNMMI Annual Meeting that, in a study of 137 adults with normal cognitive function, subjects with increased amyloid burden in cognitive neural networks were prone to impaired cognitive performance. Another study found that the APOE4 genotype reduced the age of predicted florbetapir positivity in normal aging to about 56 years, which is about 20 years younger than non-carriers.¹⁴

WHY DIAGNOSE COGNITIVE DECLINE AND DEMENTIA WITH MOLECULAR IMAGING MODALITIES?

Although no disease-modifying treatment is currently available, the correct diagnosis of a patient's cognitive deficit or dementia has therapeutic implications for current practice and long-term life planning for families. In some cases, molecular imaging modalities can contribute significantly to diagnostic refinement in cognitive decline and dementia syndromes. Clinical implications in current practice:

- In Alzheimer's disease (AD), cognitive symptomatic treatments with acetylcholinesterase (AChE) or N-methyl d-aspartate receptor inhibitors are shown to slow clinical decline. Risks of treatment of behavioral symptoms with antipsychotic drugs must be considered
- In frontotemporal dementia, the cognitive symptomatic treatments used in AD are not effective, and AChE may cause deterioration in behavior
- In dementia with Lewy bodies (DLB), treatment with antipsychotics can cause potentially lethal adverse side effects. The subtle bradykinesia/rigidity of DLB might benefit from antiparkinsonian therapy (but dopamine agonists should be avoided because of risk of psychosis)

CURRENT STATUS OF MOLECULAR IMAGING MODALITIES IN THE CLINICAL ASSESSMENT OF COGNITIVE DECLINE AND DEMENTIA

- Best practices for the use of radiotracers in the evaluation of cognitive decline and dementia are not yet clear. No guidelines have been established
- Evaluation of a cognitive syndrome by a clinician experienced in dementia is recommended before proceeding to a molecular imaging test
- A positive amyloid-positron emission tomography (PET) scan does not diagnose Alzheimer's disease (AD). A positive amyloid-PET scan is necessary but not sufficient for an AD diagnosis
- A negative amyloid-PET scan indicates that cognitive impairment is very unlikely to be caused by AD
- Florbetapir is the only FDA-approved amyloid-PET radiopharmaceutical
- ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is not approved by FDA for the dementia indication but is reimbursed by CMS for the differential diagnosis of frontotemporal dementia (FTD) and AD
- Based on research findings, FDG-PET imaging is used clinically to determine relevant areas of cortical glucose hypometabolism in the differential diagnosis of patients with dementia of unknown cause, AD vs FTD, and AD vs dementia with Lewy bodies, among

others. However, more data are needed to determine the optimal role of FDG-PET vs amyloid-PET

- Research findings suggest potential clinical roles for amyloid-PET imaging to determine the presence or absence of amyloid pathology in the differential diagnosis of AD vs FTD, mild cognitive impairment, early onset dementia, dementia with atypical or focal features, and when AD is suspected but alternative causes for cognitive decline are present, among others
- The Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association have assembled an Amyloid Imaging Task Force to develop guidelines for radiologists, neurologists, and general practice physicians, among others. They plan to issue draft recommendations to the research community in July
- Implications for the development of disease-modifying therapeutics for various dementia subtypes are significant. The use of subjects with concordant molecular imaging phenotype and clinical diagnosis could be implemented immediately to improve the purity of clinical trial populations. PET biomarkers might eventually serve as surrogate endpoints in clinical trials of potential dementia therapeutics, reducing the size (number of subjects) and duration of these trials

CLINICAL CASE STUDIES

A 68-year-old right-handed man, retired mathematics professor, presents with 5 years of insidious onset of symptoms of gradually declining cognitive function.

The patient's cognitive decline includes mild memory complaints (although he denies a significant problem), decreased decision making, geographic disorientation, poor judgment while driving, visual agnosias (eg, applying brown touch-up paint to a white wall), word-finding difficulty, "difficulty making sense of the world," financial management problems (eg, "misplaced" \$30,000, difficulty writing checks, can not present proper cash at the store or calculate tips), and losing items around the house.

Problems with activities of daily living (ADLs) include not using a washer/dryer properly (eg, puts dirty clothes in the dryer), difficulty preparing meals, needs prompting for showering, and being very disorganized (a big change for him).

He experiences no behavioral problems, hallucinations, or delusions, and presents no evidence of depression, anxiety, apathy, or personality change. Review of systems reveals night terrors and movements associated with REM sleep. Physical and neurological exams are normal except for a positive glabellar sign. Medications include a statin and vitamins. Family history is not significant.

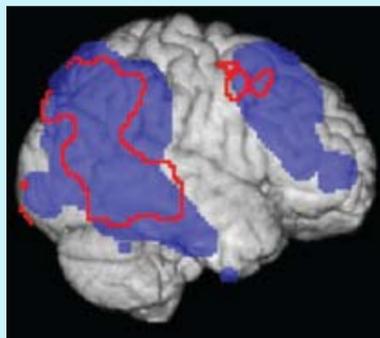
Initial diagnostic workup:

- Labs are normal: CBC, comprehensive metabolic panel (CMP), B12, and thyroid-stimulating hormone (TSH) tests
- MRI of the brain reveals mild-to-moderate periventricular white matter disease
- Formal neurocognitive testing reveals prominent deficits in executive function, attention, and calculations, and low-to-borderline scores on memory measures

Initial clinical diagnostic assessment:

- This patient meets DSM-IV dementia criteria
- Differential diagnosis includes possible underlying Alzheimer's disease (AD) with atypical presentation, dementia with Lewy bodies (DLB) or other neurodegenerative disorders, vascular dementia, or mixed AD plus vascular dementia
- The National Institute on Aging–Alzheimer's Association (NIA–AA) diagnosis is possible AD (atypical presentation) based on clinical criteria

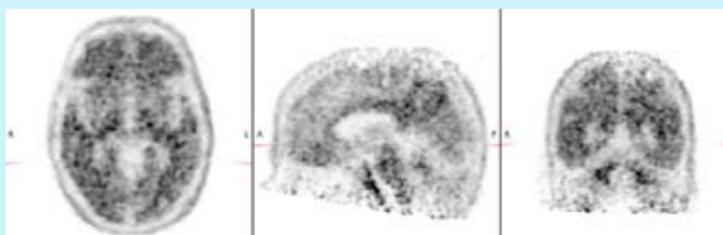
Biomarker-based diagnostic assessment is then undertaken, beginning with ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET).



FDG-PET reveals a reduction of glucose metabolism in a parietotemporal pattern, consistent with that typically seen in AD, as well as some occipital lobe involvement, which can be seen in AD but is more common in DLB. This

pattern is not consistent with a primary vascular dementia. Consistent with AD, glucose metabolism is relatively preserved in the primary motor cortex, anterior temporal lobes, and much of the frontal lobes. Blue areas depict hypometabolism in this patient compared to a normal brain dataset. Red regions represent areas of typical glucose hypometabolism seen in dementia due to AD.

With the FDG-PET study, the NIA–AA diagnosis is then refined to probable AD, intermediate likelihood with biomarker evidence. Additional biomarker-based diagnostic assessment includes amyloid-PET to determine the presence or absence of amyloid-beta.



Amyloid-PET reveals a positive finding of amyloid-beta. Contrast between the cortical gray matter ribbon and white matter is not discernible, indicating diffuse florbetapir binding to fibrillar amyloid in the gray matter.

The final NIA–AA diagnosis for this patient is probable AD, high likelihood with biomarker evidence. This biomarker-supported diagnosis allows for diagnosis of dementia due to AD with high confidence, leading to a recommendation of starting an acetylcholinesterase inhibitor, appropriate social support services and AD-specific resources, and referral to clinical treatment trials for access to experimental anti-amyloid therapies.

CLINICAL CASE STUDY

Case Study 1

REFERENCES & FURTHER READING

1. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263–269.
2. Piguet O, Hornberger M, Shelley BP, Kipps CM, Hodges JR. Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia. *Neurology*. 2009;72(8):732–737.
3. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863–1872.
4. Alzheimer's Association, Thies W, Bleiler L. 2012 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2012;8(2):131–168.
5. Bohnen NI, Djang DS, Herholz K, Anzai Y, Minoshima S. Effectiveness and safety of 18F-FDG PET in the evaluation of dementia: a review of the recent literature. *J Nucl Med*. 2012;53(1):59–71.
6. Petrie EC, Cross DJ, Galasko D, et al. Preclinical evidence of Alzheimer changes: convergent cerebrospinal fluid biomarker and fluorodeoxyglucose positron emission tomography findings. *Arch Neurol*. 2009;66(5):632–637.
7. Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. *Arch Neurol*. 2011;68(8):1062–1064.
8. Ingelsson M, Fukumoto H, Newell KL, et al. Early Abeta accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. *Neurology*. 2004;62(6):925–931.

The 2 clinical cases below exemplify the challenge of diagnostic assessment of cognitive decline and the prominent role to be played by molecular-imaging biomarkers. Cases were provided by Dr Adam Fleisher, Course Director.

A 70-year-old man with a master's degree in education and a strong family history of AD presents with cognitive symptoms including 6 years insidious onset, progressive word-finding difficulties, misplacing items, and the need for reminders for appointments. He experiences no behavioral problems or depression.

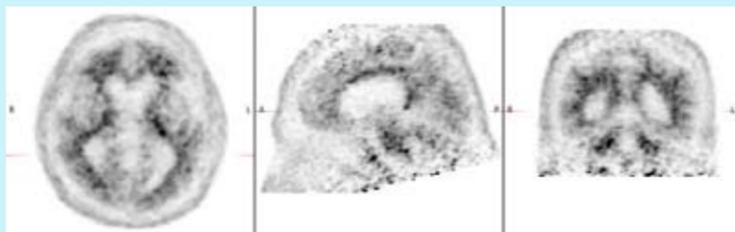
Problems with ADLs include failure to prepare taxes because it is frustrating for him. Although he manages the other finances without difficulty, he has asked his wife to be more involved. He also experiences navigational problems and prefers his wife to drive.

His medical history includes bladder cancer in remission (2006) and hypertension; he takes medications for hypertension. His family history includes late-onset AD in his father, 2 paternal aunts, a paternal uncle, and a maternal aunt. Physical examination is significant only for a positive snout reflex (a frontal release sign). Bedside cognitive testing findings include mini-mental state exam of 30/30, category retrieval of 11 animals in 1 minute, and Montreal Cognitive Assessment of 28/30.

The current clinical diagnosis for this patient is possible late MCI or early dementia caused by AD, based on clinical criteria. Next steps include ordering the following tests: detailed neurocognitive testing, a structural MRI, and labs, including CBC, CMP, B12, and TSH.

Detailed neurocognitive test results find difficulty with learning and immediate recall of verbal material, with a generally intact ability to retain what he has learned; weakness in his word-finding abilities; and intact executive functioning and visuospatial skill. These findings are most consistent with MCI due to a subcortical process.

Lab studies are then performed, and TSH/B12 are normal. A structural MRI is subsequently conducted.

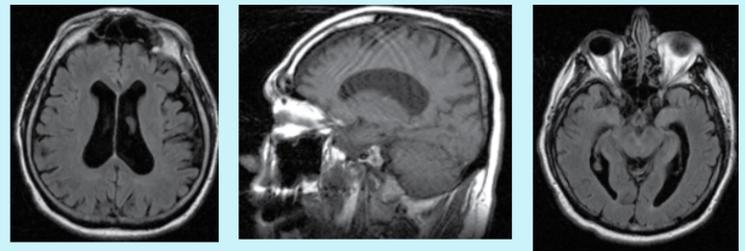


Structural MRI is reported with mildly enlarged ventricular spaces and sulcal widening, possibly consistent with normal-pressure hydrocephalus (NPH), and no significant vascular diseases.

Biomarker-based diagnostic assessment includes amyloid-PET to determine the presence or absence of amyloid-beta.

Structural MRI shows with mildly enlarged ventricular spaces and sulcal widening, possibly consistent with normal-pressure hydrocephalus (NPH), and no significant vascular diseases.

Biomarker-based diagnostic assessment includes amyloid-PET to determine the presence or absence of amyloid-beta.



Amyloid-PET is negative for amyloid-beta. Non-specific white matter uptake is seen clearly contrasted to the reduced uptake in the cortical gray matter ribbon.

Amyloid-PET is negative for amyloid-beta. Non-specific white matter uptake is seen clearly contrasted to the reduced uptake in the cortical gray matter ribbon.

The current diagnosis of this patient is MCI (non-AD), etiology unknown. Differential diagnosis includes atypical presentation of NPH, metabolic disorder, atypical variant Creutzfeldt-Jakob disease, or other neurodegenerative disorder. This negative workup for cortical amyloidosis prompts the clinician to further the diagnostic workup for these less common causes of cognitive decline, follow the patient clinically, and consider future repeat amyloid-PET and MRI scanning.

Case study summary points

- Florbetapir imaging can play an important role in diagnosis and clinical decision making in patients with questionable, atypical, or early cognitive syndromes
- There is still much to learn regarding best-use practices

CLINICAL CASE STUDY

Case Study 2

9. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119-128.

10. Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging*. 2010;31(8):1275-1283.

11. Johnson KA, Fox NC, Sperling RA, Klunk WE. Brain imaging in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012;2(4):a006213.

12. Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid- β plaques: a prospective cohort study [epub ahead of print June 27, 2012]. *Lancet Neurol*.

13. Fleisher AS, Chen K, Liu X, et al. Using positron emission tomography and florbetapir F 18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol*. 2011;68(11):1404-1411.

14. Fleisher AS, Chen K, Liu X, et al. Apolipoprotein E4 and age effects on florbetapir positron emission tomography in healthy aging and Alzheimer disease [epub ahead of print May 24, 2012]. *Neurobiol Aging*. DOI:10.1016/j.neurobiolaging.2012.04.017