When Is Neuro in Alz

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Contributing Editor
The importance of early and accurate diagnosis of Alzheimer’s disease (AD) has increased now that several effective medications are available to treat mild to moderate disease. The appropriate work-up begins with a medical history, physical examination, laboratory testing and structural imaging such as MRI and CT to rule out lesions such as tumor or vascular infarct that may cause or contribute to the patient’s degenerative symptoms. In cases where these diagnostic measures remain equivocal or point to a diagnostic designation of probable or possible AD, referral for functional nuclear imaging of the brain is the next prudent maneuver.

In recent years, numerous studies have established that PET (positron emission tomography) with fluorodeoxyglucose (FDG) is the most accurate functional modality to visualize directly and quantify focally decreased cerebral metabolism in regions of the brain characteristically associated with AD-related dementia. PET’s sensitivity, specificity and overall accuracy have been shown to far outmatch those of SPECT, or single-photon emission computed tomography, a functional measure of perfusion. (For a detailed account, see Silverman DHS. Brain 18F-FDG PET in the diagnosis of neurodegenerative dementias: comparison with perfusion SPECT and with clinical evaluations lacking nuclear imaging. J Nuclear Med 2004;45(4):594-607.)

PET’s capacity to differentiate between Alzheimer’s disease and other sources of neurodegenerative dementia such as frontotemporal dementia further adds to PET’s diagnostic utility in clinical practice. Studies have likewise demonstrated a role for PET in the early diagnosis of AD, and PET’s prognostic value in predicting the disease’s course and the likelihood of lessening its symptoms or retarding their progression following therapeutic intervention. Early detection and diagnosis of dementing illnesses—of which AD constitutes some two-thirds of cases, affecting approximately 4.5 million Americans—will play an increasing role in disease management as further advances in preventive and disease-modifying therapeutic options come into clinical use in the future.

In light of PET’s diagnostic and prognostic value, however, its infrequent use among general neurologists in cases where clinical evaluation and structural imaging (MRI, CT) indicate probable or possible AD remains to be explained. “It’s very underused in most parts of the United States and by most neurologists,” says Daniel H.S. Silverman, MD, PhD, head of the Neuronuclear Imaging Section in the Biological Imaging Division of the University of California Los Angeles. “Those currently referring for PET probably constitute at most 5-10 percent of practicing neurologists.”

That paucity of participating neurologists may change now that Medicare has approved the reimbursement of PET in cases of probable or possible mild to moderate AD. The number of neurologists who refer for PET may likewise increase as data from recent and ongoing studies attesting to its diagnostic value are disseminated in the neurological and radiological literature. The efficacy of current medications and presumably of those under investigation in curbing AD’s progression lends additional impetus to making use of PET scanning in appropriate diagnostic settings.

Why Is Early Treatment Best?
Perhaps the best argument in favor of the use of PET at the earliest stage of AD-related dementia is that it allows the neurologist to initiate treatment on the most sound diagnostic basis possible (besides autopsy) at a point when that treatment would do the most good. There are both physiological and empirical reasons why this is so.

Physiologically, degenerative dementia such as AD causes irreversible dysfunction and death of neurons that renders the affected tissue beyond the reach of pharmacologic treatment. This is why cholinesterase inhibitors—donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl)—are indicated solely for mild or moderate AD. Within a few weeks of starting these drugs, glucose metabolism can increase, particularly in the frontal parts of the brain. While only a minority of patients will actually see improvement in behavioral or cognitive function, many more will experience at least a decrease in the rate of deterioration. Studies of large groups of patients suggest that these agents are helpful in this regard, although it is difficult to determine whether a particular patient is not declining as much as he or she otherwise might in the absence of treatment. By the time AD reaches the severe stage, the widespread irreversible death of neurons renders these medications largely ineffective.

There are also empirical studies that document the benefit of early treatment with cholinesterase inhibitors when AD is still in the mild to moderate stage. Even among patients who are start-
ed on treatment at this stage, a delay of six months before the
start of treatment means these patients will never achieve the
functional benefits obtained by those started at an earlier point.

What's more, there is a close correlation between glucose
metabolic patterns seen on PET scan and the patient's function-
ing. “There's an outstanding correlation,” says Murray
Grossman, MD of the University of Pennsylvania School of
Medicine's Department of Neurology. “There's a long history of
studies that began 20 years ago that show a very reliable correla-
tion between reduced activity in parts of the brain affected by
AD and difficulty with cognitive or social functioning.”

Subsequent PET scans following treatment with cholin-
esterase inhibitors will exhibit changes in PET patterns. “The
glucose metabolism will increase, particularly in the front part
of the brain, after a few weeks of therapy,” says Dr. Silverman.
Although only a minority of patients get significantly better with
these drugs, a majority have a decrease in the rate of deteriora-
tion. “We know by statistical studies on large groups of patients
that treatment is helping, but it's hard to know the effect in an
individual patient,” he says.

Although clinical stability instead of decline amounts to ben-
eficial treatment, patients and caregivers may be dissatisfied that
clear functional improvement has not been achieved. PET scan-
ing helps verify the beneficial effect of treatment to skeptical
patients and caregivers.

**Differential Diagnosis**

PET scan is the ultimate definitive measure in a differential diag-
nostic evaluation which begins in the clinic with a patient histo-
ry that may suggest either "possible" or "probable" AD. The two
speculative diagnostic designations warrant explication. “To
make the diagnosis of probable Alzheimer’s disease, first the
patient has to be confirmed to actually be demented, which pri-
marily means two things,” Dr. Silverman explains. “First, they
have multiple cognitive domains impaired: memory symptoms
plus something else, such as inability to exercise good judgment
or diminished abstract reasoning ability or visuospatial ability,”
he says. “Things that they normally would have done better in
the past are declining along with memory.”

One potential drawback is that it may be difficult to elicit
from patients an accurate and useful history of their current cog-
nitive and behavioral status. “The patients may be in denial
themselves,” Dr. Silverman says. “They may have noticed some
worrisome cognitive changes but might be unwilling to admit it
out of either denial or fear of having their driver’s license taken
away or similar restrictions they might be subjected to.” The
more intelligent and high-functioning patients are to begin with,
the further they can evolve before they’re less able to hide the
symptoms from other people, even though they’ll notice a big
difference in their own level of functioning. “What often hap-
pens is that it’s not the patient per se that the most important
part of the history is elicited from, it’s their family members or
close contacts,” he says. The designation of probable AD requires
a second criterion. “Patients have to have deteriorated to the
point that the condition impairs their ability to function—in a
social, personal and/or professional setting,” Dr. Silverman says.

Even when met, these criteria do not alert the clinician to the
dementia’s specific cause. The path of the differential diagnosis
now turns to arriving at the specific cause after ruling out vari-
ous conditions that likewise can cause dementia. Since AD
accounts for about two-thirds of all dementia cases—twice as
many as all others combined—a simple guess of Alzheimer's dis-
ease at this point places the odds in your favor. Assuming your
diagnostic sophistication extends beyond guesswork, you must
now eliminate many other common causes of cognitive impair-
ment or behavioral changes, such as depression, drug-drug inter-
action, hypothyroidism, B-12 deficiency, anemia, liver disease,
kidney disease, cerebrovascular disease and frontotemporal
dementia.

Simple laboratory tests can eliminate many of these condi-
tions. Aiding the differential diagnosis between AD and fron-
totemporal dementia is the fact that the latter tends to bring
about behavioral and language changes far more than memory
changes early on, whereas Alzheimer's disease is characterized by
the opposite pattern. This in itself contributes to the diagnosis
but is still insufficiently definitive.

If you find that the patient is demented but cannot identify
anything else that may be to blame, you have arrived at a diag-
nostic designation of probable AD; you have yet to determine in
a positive way that the patient does in fact have AD.

Possible AD refers to situations in which the patient's history
fits the pattern of Alzheimer's disease—and that this is the pre-
dominant consideration at this stage—but there are other condi-
tions present which may cause or contribute to the patient’s
dementia. “For example, if the person has enough cerebrovascu-
lar disease on MRI that there would be a question about whether
or not they have cerebrovascular dementia, or if they had some
laboratory abnormalities that could be contributing, that would
lower the designation from probable Alzheimer’s to possible
Alzheimer’s,” Dr. Silverman says. “It’s less definitive, a less-clean
case. If you don’t include the possibles, you’ll miss a lot of peo-
ple who actually have Alzheimer’s, because there are plenty of
people who have multiple conditions in addition to AD, greatly
lowering your sensitivity.”

Moving beyond the patient history, physical and neurologic
examination and laboratory testing, the next step in narrowing
the diagnostic possibilities is to order structural neuroimaging
such as MRI or CT scan. About 90 percent of the PET scanners
being sold today are also equipped to perform CT scan, allowing
for structural and functional imaging in one session.
Structural imaging allows you to rule out non-neurodegenerative diseases such as tumors, vascular changes (bleeding, hypertension, infarcts) and normal-pressure hydrocephalus, and to detect structural abnormalities that are consistent with a diagnosis of Alzheimer’s disease. “You’re looking for significant hippocampal atrophy in patients with Alzheimer’s disease, using the distribution of atrophy in the temporal lobe to distinguish between Alzheimer’s and related conditions, such as frontotemporal dementia,” Dr. Grossman says.

A finding of cerebrovascular disease on MRI may throw the physician off course in seeking the correct diagnosis. “Patients often get misdiagnosed as having cerebrovascular dementia when that’s more of an incidental finding,” Dr. Silverman says.

In fact, the role of structural imaging with MRI or CT scan is generally limited to the exclusion of causes of dementia besides AD. This curtails their diagnostic value in cases where the patient does in fact have AD, which may initiate few if any characteristic structural changes. “The reason that both CT and MRI are not particularly valuable is because with most of the people who have Alzheimer’s disease, there’s nothing to find in the brain that’s very specific for it,” Dr. Silverman says. “The person can look perfectly normal in the early stages, or they can develop atrophy, but the atrophy can occur as a consequence of a whole host of diseases that cause dementia. There’s a huge overlap not only between normals and diseased people but especially between people with different diseases.”

In general, with any number of neurodegenerative diseases in which the brain doesn’t use as much glucose compared with normal individuals, “it shows up on PET as areas of gray instead of black when looking at a black-on-white scan,” Dr. Silverman says. “If you’re looking at rainbow scales, it shows up as being a lower color on the rainbow, indicating areas on the PET scan where less glucose is being taken up.”

A key differential diagnosis for which PET scanning is especially useful is that of AD versus frontotemporal dementia. Autopsy studies have shown that most patients who turn out actually to have had frontotemporal dementia had been clinically diagnosed instead with AD. “That has significant implications, because the drugs that are used to treat Alzheimer’s actually can exacerbate the symptoms of frontotemporal dementia,” Dr. Silverman says. “Some doctors are overconfident in their ability to diagnose Alzheimer’s disease.”

The different patterns seen on the PET scan are quite different in AD compared with frontotemporal dementia, and this difference is obvious and specific especially in the early stages of disease. “Alzheimer’s will involve the inferior parietal cortex and posterior cingulate cortex,” Dr. Silverman explains. Adds Dr. Grossman, “corticobasal degeneration also typically presents with disease in a parietal distribution, but only AD has a combination of reduced parietal and reduced mesial temporal glu-
cose uptake.” AD largely spares the basal ganglia, thalamus, cerebellum and cortex that mediates primary sensory and motor functions. Studies have shown greater sensitivity to disease severity involving the parietal lobe rather than temporal lobe deficit.

“Frontotemporal dementia will have just the opposite pattern, where the frontal lobes of the brain and the front part of the temporal lobes are decreased early on, and the posterior cingulate isn’t affected at all,” Dr. Silverman says. “As these conditions advance the patterns become less specific, because more and more of the brain becomes affected. The fact that the differences are most apparent early on—assuming they are detected at that point—actually turn out to be fortuitous: one, because that is when the diagnosis is otherwise most difficult to make clinically; and two, that’s when you want to initiate treatment, at the earliest stage possible.”

Other forms of dementia produce characteristic patterns on PET. Dementia secondary to cerebrovascular disease creates a pattern of focal cortical and non-cortical inhomogeneities (which correspond to areas of infarction on MRI). Focal cortical inhomogeneities unmatched by MRI findings are consistent with numerous primary neurodegenerative disorders, such as AD itself as well as Pick’s disease, other frontotemporal dementias, dementia with Lewy bodies, Parkinson’s disease, Huntington’s disease, or progressive subcortical gliosis. A pattern of bilateral temporoparietal hypometabolism distinguishes AD from age-matched normals as well as from vascular or frontal lobe dementias. Neuroscopic uptake correlates not only with dementia severity and specific patterns of AD-related cognitive deficit but also with regional densities of neurofibrillary tangles.

When to Order PET
Different authorities will give you different answers about when is the appropriate time to refer a possible or probable AD patient for a PET scan. Based on what the scientific evidence indicates, every patient for whom a specific cause has not been identified for their dementia would be likely to benefit by obtaining a more definitive diagnosis. Short of autopsy, functional imaging by means of PET will yield the most definitive diagnosis possible, particularly when compared with clinical evaluation, structural imaging and SPECT. In fact, PET can detect regional cerebral metabolic changes associated with early AD even before the onset of symptoms.

A large investigation of patients with suspected early or mild AD found that PET’s sensitivity was 95 percent, its specificity 71 percent, and its overall accuracy 89 percent. These values are consistent with the ranges found in a broad review of other PET studies. Among studies comparing PET with SPECT, an investigation of AD patients with mild symptoms found that PET’s accuracy was 15-20 percent better than that of SPECT. SPECT scan is not as accurate because the best SPECT cameras provide less spatial resolution than that of PET cameras; another reason is that blood flow as seen on SPECT is not as severely affected as the glucose as seen on PET. “The PET scan is going to be superior to SPECT scan every time,” Dr. Grossman says.

The scientific evidence suggests that clinicians should consider ordering PET for two groups of patients:

1. Those with mild or moderate cognitive impairment who meet the criteria for dementia and for whom a thorough medical work-up and structural imaging have not identified a cause.
2. Those with increasingly progressive mild or moderate cognitive impairment following a thorough medical work-up along with appropriate treatment for any positive findings.

PET Sounds
The diagnostic value of PET scans in the setting of probable or possible Alzheimer’s disease has been well-established. Neurologists who avail themselves of this highly accurate nuclear neuroimaging modality can manage their Alzheimer’s patients with the greatest assurance presently feasible that their diagnosis is definitive and provides a sound basis for appropriate treatment. The test is easy to perform and comfortable for the patient, and provides characteristic patterns—especially early on—that are invaluable in ruling out other causes of dementia.

Now that Medicare reimburses for PET scans for those with mild to moderate Alzheimer’s disease, clinicians should face no economic obstacle to order the test when the necessity of PET is properly documented. As new treatments emerge in years to come, PET’s diagnostic value for patients with mild or moderate AD—those most likely to benefit from early treatment—will no doubt increase. PN