Q&A: Alzheimer's Disease and Amyloid PET Imaging

June 01, 2015 | PET CT [1], Contrast Agents [2], Molecular Imaging [3], Nuclear Imaging [4]
By Liza Haar [5]

A new study of amyloid PET brings imaging to the forefront of research for Alzheimer's disease.

In April, the ACR and the Alzheimer’s Association announced a four-year, $100 million research study to determine the clinical value of brain amyloid PET in diagnosing Alzheimer’s disease and other types of dementia.

The Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study is an effort to prove to CMS that PET amyloid imaging can lead to improved health outcomes, and therefore warrants coverage. Diagnostic Imaging spoke with a member of the IDEAS leadership team, Barry A. Siegel, MD, of Washington University, about why this study is important.

**What's the history of amyloid PET imaging?**

Amyloid imaging agents have been around for a number of years with a large amount of the research to date using carbon 11 compounds’ the one that's been most widely used is referred to as Pittsburgh Compound B or PIB. PIB has been comprehensively studied at many institutions around the country that have compared the amount of amyloid in the brain in people of various ages. They looked at its build-up as a function of age and compared it across different disease states. They have looked at patients who were amyloid positive and followed them over time to see whether they develop typical clinical patterns of Alzheimer’s disease (AD). So amyloid imaging has been well established as a robust biomarker of the presence of abnormal amyloid deposition in the brain, which is one of the key pathologic features of AD.

The presence of amyloid pathologically or the detection of amyloid by PET imaging, is not in and of itself diagnostic of AD, but the absence of amyloid goes a very long way in a patient who is having symptoms of either mild cognitive impairment or early dementia to exclude AD as the basis of that dementia. It doesn't give you the precise alternative diagnosis but it does tell you that AD in a specific clinical context that otherwise fits with AD is quite unlikely.

So based on the results with PIB, there was a great deal of interest in development of PET agents labeled with fluorine-18. This began first with Avid radiopharmaceuticals (Eli Lilly), which received FDA approval in 2012 for the first PET imaging agent, Amyvid. There have been two subsequent approvals: GE’s Vizamyl, and Piramol’s Neuraceq.

Because of considerable clinical interest in amyloid imaging, the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer’s Association developed appropriate use criteria with well-defined indications for clearing up confusing clinical situations and aiding in patient management. The criteria also provided guidance on when use of amyloid imaging was inappropriate.

Eli Lilly then asked CMS to provide coverage for amyloid PET. One of the unique features of PET
coverage by Medicare is the exclusion policy, namely that if Medicare doesn’t say a use of PET is covered, it’s not covered. Until very recently, any new PET radiopharmaceutical had to undergo a complete national coverage analysis before a decision could be made about coverage. CMS evaluated the evidence and decided that they didn’t think amyloid imaging was ready for prime time, but the final decision memorandum did say that CMS thought it would be reasonable to cover amyloid imaging under conditions of coverage with evidence development (CED) for patients enrolled in appropriate clinical trials or registries where amyloid imaging was being used to aid with diagnostic uncertainty or to help get patients into therapeutic trials that would be designed to address treatment of AD.

Over the subsequent 18 months, the Alzheimer’s association led an initiative to bring several interested stakeholders together to develop a CED program. I became involved, as did Bruce Hillner, because of our experience with another CED effort, the National Oncologic PET Registry. We worked with a group of people with other backgrounds and greater expertise in the care of patients with dementia, the Alzheimer’s Association, and other professional societies and we began to develop some concepts that we have now iterated several times with CMS. So, we now have a protocol that CMS says is approvable, with some additional requirements for clarification, to be launched as a CED program. With that approval finally in hand, we are now charging ahead to secure all of our funding sources and, once we’ve done that, we’ll start design and programming of electronic case report forms, site recruitment, training, and hopefully close to the end of this year or early January 2016, the IDEAS study will be up and running.

**What is the process for diagnosing or excluding Alzheimer’s or dementia at this time?**

It’s a complicated process, it’s largely clinical diagnosis. The only certain way that you can make the diagnosis clinically is by autopsy or by a biopsy of the brain. Pathology is the only absolutely certain way but there are well-defined criteria for making a clinical diagnosis. However, there’s general agreement that even experienced dementia experts will be wrong about the diagnosis up to 25% of the time, so better diagnostic approaches are necessary. The standard clinical diagnosis consists of historical information; a longitudinal period of observation indicating that the patient’s cognitive function is worsening over time, often reported not only by the patient but by people close to the patient; some sort of structural imaging of the brain, usually CT or MRI, more often MRI, to make sure there’s not some other obvious cause like normal pressure hydrocephalus or a brain tumor or multiple previous strokes that went unrecognized that could be causing the symptoms; some fundamental, fairly simple laboratory testing to find some treatable metabolic problems that are potential causes of dementia, including tests for thyroid function, vitamin B12 measurements because there are syndromes associated with deficiency that can act like dementia-like states, and a few other things; and then careful examination by a neurologist, sometimes a neuropsychological examination. You put all of that together and you are usually able to conclude that a patient has cognitive impairment of some degree and then based on subtle differences in what domains are impaired, in terms of cognitive function, you may conclude that a patient has one disease versus another. For example, a patient may have frontotemporal dementia, of which there are several different variants, rather than the more common AD. This is one common dilemma, but there’s a very broad differential of things that are included.

Medicare provides coverage of FDG PET for distinguishing frontotemporal dementia from AD because there are distinctive patterns of those two disorders. It is very likely that amyloid imaging will actually prove to be somewhat more sensitive because the changes of amyloid deposition in the brain occur before the changes in metabolism indicating that neurons have actually started to significantly lose function, but, in many ways, the two tests may prove to be complementary, one proving that amyloid is present, the other proving that there are metabolic aberrations in the brain indicating that injury has already occurred.

There is a whole new class of radiopharmaceuticals for detection of Tau protein, which is another good biomarker of neuronal damage; the approach to patients with dementia is starting to get even more complicated in terms of available options. There is other testing that one can do for AD, for example by doing lumbar punctures and analysis of abnormal proteins in the spinal fluid but those are not routinely done clinically and not routinely paid for yet, as a general rule.

**Would you say that amyloid imaging is detecting something brand new that we don’t already have or it’s better detecting something that we can detect in another manner?**

The only other way to detect it now or infer its presence, other than by autopsy or brain biopsy, is by the cerebrospinal fluid tests, so it’s providing unique information. The FDA approved amyloid imaging as a reliable biomarker of the presence of amyloid in the brain and I think what the community is struggling with at large is understanding exactly how its use fits appropriately into...
clinical practice; neither the nuclear medicine community that would be performing the test, nor the neurology and psychiatry community that would be ordering the test has a lot of experience with its use in practice and, to some extent, that is part of CMS’ reluctance in covering it. CMS has come down rather hard saying that they aren’t convinced that using amyloid to help manage patients with dementia will improve their outcomes, but investigators who have a lot of experience with amyloid imaging don’t agree with that; they think it will lead to a more specific diagnosis and allow for better selection of drug therapy and also allow avoidance of inappropriate drug therapy. So, for example, the cholinesterase inhibitors that are used in AD are not good to use in frontotemporal dementia because they have more side effects, so helping to make that distinction, providing patients with appropriate counseling to avoid some of the adverse things that can happen to people that are losing cognitive function and just getting people and their families adjusted to a dementing illness so that they understand what’s in store for them is very important to patient management.

Some might say if we can’t cure it, what good is having this information?
The real question is whether survival is the only improvement in patient outcome that is clinically meaningful. Part of what the IDEAS study is going to address is just that. We are basically studying two things. First, we have a short term aim to see, whether knowing the patient’s amyloid status, leads treating physicians to alter their management. Referring physicians will record their plan for treatment before the scan and, unlike what we did in NOPR—where their plan after the scan was captured, in IDEAS we are going to capture actual management after three months to determine how often management changed. The management changes can include changing medications to avoid inappropriate side effects or to make sure the patient is on the best medications to slow the course of cognitive decline, and providing appropriate counseling to help people deal with normal life activities. These are all things that can lead to some benefit to the patient. The second objective of the study, the more complicated part, will involve a comparison of the Medicare claims of patients who have had amyloid scans with a matched cohort of Medicare patients who haven’t, and measuring the rates of hospitalizations and emergency room visits. The hypothesis is that a better diagnosis will lead to better management, which will, in turn, lead to less frequent hospital and emergency room visits, a direct benefit both to patients and the health care system.

The need for amyloid imaging will changes substantially once there is a specific therapy for AD that is based on either reducing or stopping the build-up of amyloid in the brain, since one wouldn’t want to give the therapy if the patient isn’t documented to have amyloid in the brain. Using amyloid PET as a biomarker to say ‘the target of interest is present, and therefore this patient is an appropriate candidate for this type of therapy’ would really be a game changer in terms of Medicare coverage. Once such a therapy has been shown to be safe and effective and has been approved by the FDA, it becomes essential to have a diagnostic test that reliably says who should and should not receive the treatment. The treatment is likely to be expensive and will have some adverse effects, so you want to make sure you are giving it to patients most likely to benefit.

If CMS is holding onto its position that coverage depends on improvement of outcomes, what are the acceptable outcomes?
CMS has more or less indicated that a change in management per se is not a convincing improvement in health outcomes. CMS would certainly accept a mortality endpoint, but it’s going to be a real challenge to try to address in any kind of meaningful study to show a difference in survival from a diagnostic test. They also would consider studies that clearly look at rates of cognitive decline, but those are going to require randomized controlled designs for the most part to show their effect; there is another CED proposal that is going to be looking at that. One can also, in a randomized design, look at things like quality of life.

What do you expect that this study will conclude?
I expect that this study will conclude what we set out to show, that the use of amyloid imaging changes patient management, that those changes in management actually do lead to reduction in hospitalization rates and emergency room visits, and that this represents an improved outcome for Medicare beneficiaries. However, my instinct also tells me, over the same time interval frame it’s going to take us to complete this study, that one of the anti-amyloid agents is going to hit a home run and get approved by the FDA, and the whole landscape may change very quickly. Recent interesting evidence for this from a Biogen Idec study showed, for the first time, that the use of a drug in people with prodromal or mild Alzheimer’s disease quantitatively reduced the amyloid burden in the brain on PET, but also clearly resulted in cognitive impairment compared to a control group that got placebo.

What kind of training would this require for radiologists?
Like any new radiopharmaceutical introduced into practice, interpreting physicians will have to learn
about the biodistribution of the agent and how to read the PET scans. Amyloid images are neither the easiest nor the hardest scans to read. All three vendors have training programs, which was required by the FDA for approval. There are online training programs from each of the vendors, and they also all provide additional support from experts to individual facilities starting to ramp up amyloid imaging. I don’t think the learning curve here is going to be any worse than it is for other new thing that come along in diagnostic radiology or nuclear medicine.

We plan to require in the IDEAS study that the participating PET facilities are all accredited by one of the several current accrediting bodies and that all of the readers who will be reading these scans will have taken the vendor-specific training for whichever amyloid imaging agent they plan to use.

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