



Tracing a Future for Diagnostic Imaging in AD

An insider offers an update on the progress of development and clinical challenges that remain.

Not too long ago, a confirmed diagnosis of Alzheimer's disease was possible only via post-mortem examination of a patient's brain. The presence of tell-tale amyloid plaques and neurofibrillary tangles (tau filaments) confirmed that the dementia a patient experienced in life was a consequence of Alzheimers and not some other pathology. Today, *in vivo* diagnosis of AD through radiographic imaging occurs in the research setting, and it could soon be a reality in neurology practices across the country.

Current Research

Promising clinical results for the *in vivo* diagnosis of AD have already been obtained through the use of PET imaging to measure the decrease in Glucose metabolism in the brain of patients affected by AD. However, a more direct measure is made possible with chemical "tracers" that will "highlight" either plaques or tangles in the brain. To date, developmental research efforts have yielded best results targeting amyloid- β with limited progress toward identification and use of tau markers, says Hartmuth Kolb, PhD, Vice President of Biomarker Research at Siemens Medical Solutions, which develops and markets PET and other imaging systems.

Despite promising advancements reported both in the medical literature and in the lay press, widespread clinical use of PET for diagnosis of AD may still be several years off, according to Dr. Kolb. One obstacle to clinical use is the challenge of demonstrating the efficacy of imaging. FDA requires that developers correlate PET evidence of amyloid burden with post-mortem staining of subjects, "to show that the image correlates with the hallmarks of the disease," Dr. Kolb says. Significant time may lapse before developers are able to acquire sufficient post-mortem confirmatory data to "prove" the benefit of imaging.

To ease the approval process, Dr. Kolb notes that many developers will probably initially seek an FDA indication for their markers (the four most promising tracers are described

in the sidebar below) to exclude a direct diagnosis of AD in a patient with dementia. When the neurologist is uncertain about the cause of dementia, imaging could be used to determine the amyloid burden in the patient's brain. Lack of significant amyloid could rule out the AD diagnosis and permit the physician to pursue other diagnoses and treatments.

Using PET amyloid imaging as a positive test for AD currently presents some clinical challenges, Dr. Kolb notes, because there is lack of consensus regarding the correlation of amyloid to disease status. Dr. Kolb says trials thus far have identified a false-positive rate of up to 10 percent or more for amyloid imaging; some patients have amyloid deposits in the brain but do not currently have or ever develop AD symptoms over the course of monitoring. Furthermore, there is no clear correlation between amyloid load and severity of AD symptoms.

Potential Benefits

Despite practical challenges, the goal for diagnostic imaging in AD is to be able to identify early disease. Though scans won't be cheap, they could actually save healthcare dollars. "We don't know how much costs could change when adding a tracer to scanning in the clinical setting," Dr. Kolb admits, "but by identifying Alzheimer's disease in its earliest stages before it becomes a bigger problem and permitting the use of drugs to delay or stop progression, it could save money in the long-run." It could come down to a difference in "thousands to scan versus tens of thousands to care for an advanced AD patient," he says.

Dr. Kolb cautions that the use of imaging to detect pre-symptomatic AD may depend on future development of tau tracers, because, "amyloid may not be helpful for early diagnosis. Once you show symptoms, the brain may be almost fully destroyed by amyloid." Given what Dr. Kolb calls a "disconnect" between amyloid burden and clinical disease status, it is unclear if, when, and how therapy should be initiated in

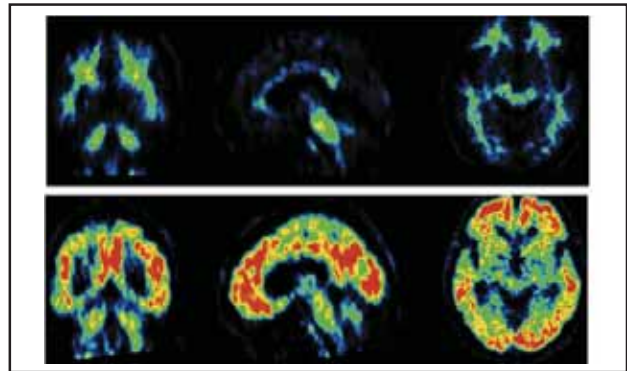
patients who show evidence of amyloid on imaging but do not have clinical symptoms of dementia. Importantly, research into new therapies is progressing simultaneously. Potentially, knowledge gained from AD imaging could contribute to therapeutic development.

Other Avenues

Investigation into the development and use of tau tracers is ongoing. “The most obvious thing you look for in the brain is amyloid,” Dr. Kolb says, “Just now people are beginning to realize that tau is important.” Initiatives are underway in this arena.

MRI, including functional MRI (fMRI), is another area of investigation for the diagnosis of AD. Functional imaging may detect changes in brain function, particularly with regard to episodic memory and other cognitive capabilities frequently affected by AD. Recent studies, based on the National Institute on Aging’s (NIA) Alzheimer’s Disease Neuroimaging Initiative (ADNI), have revealed that hippocampus volumes in patients, as measured by MRI, in conjunction with memory tests, are a very robust set of predictors for distinguishing people who progressed from Mild Cognitive Impairment (MCI) to AD.

PET scans using fluorodeoxyglucose (FDG), a short-lived radioactive glucose molecule, is also being used investigatively to find and monitor changes in brain activity in dementia



18F-AV1/BAY 94-9172 imaging of amyloid plaque. Photo property of Avid.

patients. A recent ADNI study has shown that MCI patients who showed low glucose metabolism in the brain, as measured by FDG-PET, and who scored poorly in memory tests, were likely to convert to AD.

FDG-PET alone may also be used over time to identify and monitor changes in the structure and function of brains of patients with dementia. For example, declines in regional cerebral glucose metabolism (rCMglc), measured by FDG-PET, correlate with a progression of Alzheimer’s. With any of these latter methods, research still seeks to determine which changes are specific to AD. PN

Amyloid Tracers in Development

Pittsburgh Compound-B (PIB). One of the first and best-known of the investigated tracers, the carbon-11 compound developed at University of Pittsburgh targets amyloid-beta and has been shown to have pathological correlation. However, Dr. Kolb notes that the compound’s short half-life of about 20 minutes makes it somewhat impractical from a clinical standpoint. He also says that larger studies are needed to confirm the utility of the agent seen so far.

F-18 labeled PIB. This second-generation tracer in development by GE has been shown to have a similar affinity for uptake by amyloid but a longer half-life than PIB.

AV-1 (18F-AV1/BAY 94-9172). This tracer, licensed to Bayer-Schering by Avid Radiopharmaceuticals, has shown promise for highlighting amyloid and is currently in Phase II trials.

AV-45 (18F-AV-45). This compound in development by Avid is currently in Phase III trials and could be approved by the FDA within a few years.

18F-SMIBR-W372. This novel amyloid tracer developed by Siemens is currently being evaluated in early-stage clinical trials.