Amyloid Imaging Revs Up Alzheimer’s Research

A new brain-imaging technique that detects amyloid plaques in living people is already speeding the search for Alzheimer’s treatments, raising hopes that its symptoms might someday be prevented.

By Jim Schnabel

In the second-largest hospital chain in Japan, patients suspected of having Alzheimer’s disease are often given what might be called a “virtual autopsy” of the brain.

The procedure begins in a lead-shielded radio-pharmaceutical facility. Technicians place a special tracer compound in the path of an atom-smashing cyclotron, giving the tracer a mild and brief radioactivity. Radiology staff then hustle the tracer compound into a nearby imaging facility, and inject it into the bloodstream of waiting patients. When the tracer molecules enter the patients’ brains, they cling, by design, to any deposits, or “plaques,” of clumped-together amyloid-beta protein—one of the classic pathological signs of Alzheimer’s. During the narrow window of opportunity before the tracer’s emissions grow dim, the medical team places each patient’s head into a standard positron-emission tomography (PET) scanner, whose scan shows in 3-D the places in the brain where the tracer has clung.

In this way, for the first time, doctors can effectively see the amyloid plaques in the brains of their living patients. If the scan shows a heavy plaque load in a person with memory problems, then the person is likely to have Alzheimer’s. If the scan shows little or no plaque load, then the patient’s memory problems probably have some other cause.

“Until the advent of amyloid imaging, we had to wait until the person died and came to autopsy to verify that they had plaques,” says John Morris, who directs the Alzheimer’s Disease Research Center at Washington University Medical School in St. Louis and has worked extensively with amyloid imaging techniques. “So this represents a revolution in our ability to understand the development of the disease process.”

The first amyloid imaging tracers are expected to be approved by the FDA for use in U.S. hospitals in 2011. Their availability will mean that doctors can be more certain in diagnosing Alzheimer’s, which will be particularly important when therapies are available to slow or stop the disease. Many researchers believe that the therapies currently in development and testing won’t work unless begun very early in the disease process, perhaps even before a person’s memory problems are evident. Techniques such as amyloid imaging may soon be used to provide this early warning.

“I think its real value in the future will be its predictive value,” says Reisa Sperling, a neurologist and neuro-imaging specialist who directs the Center for Alzheimer’s Research and Treatment at Brigham and Women’s Hospital, part of Harvard Medical School. Sperling also is a member of the Dana Alliance for Brain Initiatives.

By pairing a new method of scanning for amyloid with standard functional magnetic resonance imaging (fMRI), shown here, researchers found that people who had more amyloid plaque buildup showed a type of abnormal brain activity typically seen in people with dementia.

A New Diagnostic Tool

Pathologists have known since the 1960s that a yellow dye known as thioflavin T sticks to amyloid plaques in autopsied brain tissue. In the 1990s, two researchers at the University of Pittsburgh, William Klunk and Chester Mathis, started investigating compounds that might work as amyloid PET

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tracers, and eventually focused on compounds related to thioflavin T. The second compound they developed for human testing—“Pittsburgh Compound B,” or “PIB”—worked well in an initial study of 25 subjects, published in 2004, and the field of amyloid brain-imaging was born. (Dana Foundation grants to Julie Price and John Morris helped support this line of research)

PET tracers lose their radioactivity quickly, and that is especially true of PIB, which becomes useless within a couple of hours. The cyclotron that generates PIB’s beacon-like positron-emitter, carbon-11, must be located within walking—or running—distance of the brain-imaging facility. “We have to time the elevators when we use PIB,” says Sperling.

PIB imaging therefore can be used only in the few dozen medical research centers worldwide that have their own PET-tracer-making cyclotron on site. “It’s going to see very limited clinical use,” says Mathis. But following the invention of PIB, Mathis and Klunk and other researchers developed new amyloid-binding tracers that incorporate a more standard and longer-lived positron-emitter, fluorine-18—which can be used in any hospital with a PET scanner. At an Alzheimer's research conference in Hawaii in July of this year, researchers reported that their imaging with one of these new tracers, florbetapir, was 100 percent accurate in detecting amyloid load—as verified at autopsy—in 35 elderly patients, and also showed no “false negatives” in 47 young and healthy subjects.

Amyloid imaging won’t immediately become a primary tool for diagnosing Alzheimer’s. PET imaging is inherently expensive—about $3,000 per scan—and insurers may refuse to reimburse for its use in most cases. “In about 10 percent of the dementia cases in my clinic, I’ll see someone who’s only 55 or 60, or is older but has much more language trouble than is normal in early Alzheimer’s, and then it might be useful,” says Sperling. “But it's not clear to me that it’s going to be cost effective for the typical Alzheimer’s case.”

That calculation could change dramatically if an anti-amyloid-beta drug was shown to be effective against Alzheimer’s.

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Then it will make much more difference to determine whether someone has amyloid-based neurodegeneration or not,” says Sperling.

The Early Warning Scan?
Amyloid imaging will make an even greater difference if it can detect the disease before symptoms begin, thus enabling the prevention of Alzheimer’s if suitable therapies become available. It isn’t yet clear that a buildup of amyloid always presages dementia, but the evidence so far suggests a strong relationship between the two. In July 2009, for example, Sperling and her colleagues reported on a study of older people who were either cognitively normal or had the mild cognitive impairment (MCI) that can be a precursor of dementia. Using amyloid imaging, paired with functional magnetic resonance imaging (fMRI) to measure brain activity, Sperling’s team found that amyloid plaque buildup—even in people whose cognitive skills seemed unimpaired—correlated strongly with abnormal, memory-related cortical activity such as that typically seen in dementia cases. “These functional changes were occurring probably ten years or so before they developed dementia,” says Sperling.

Morris and his team have found similar results. In a study published in December 2009, they performed amyloid imaging on 159 older people who had no signs of cognitive impairment, then followed them for three to four years. “Although our follow-up time was on average relatively short, those adults who were shown to have plaques by amyloid imaging were at much higher risk of becoming demented within that follow-up period than those who were amyloid-negative,” Morris says.

Longer-term follow-ups of these patients will clarify this risk, but Morris and Sperling and many other researchers already suspect that there is a “preclinical” phase of Alzheimer’s, lasting a decade or more, in which no symptoms are noticed, but amyloid plaque builds up. The plaque buildup eventually levels off, more or less, but by this time other disease-driving processes are under way, including inflammation, the spread of pathologic forms of the protein tau, and the general withering-away of neurons. As these secondary processes appear, dementia sets in and becomes virtually unstoppable. “Once dementia occurs, amyloid may no longer be the major driver,” Morris says.

If this is so, then it would seem that the ideal time to use amyloid imaging is in the early, preclinical phase. But to do that now on a large scale with elderly people would be controversial, says Mathis. It isn’t yet clear that amyloid buildup inevitably leads to dementia, and there isn’t yet a useful therapy that fearful, “amyloid-positive” people could take. “About 20 percent of cognitively normal elderly subjects in their sixties will be positive on PIB scans,” Mathis says. “For subjects in their eighties the figure is more than 50 percent.”

In the realm of Alzheimer’s drug research, however, the screening of ordinary elderly people with amyloid imaging is about to become routine. Most of the drugs currently in the development pipeline target amyloid beta. And if amyloid beta drives the disease mainly in the preclinical phase, then drugs ideally should be tested in people whose disease is still in this phase.

“I predict that within a couple of years we will see clinical trials with people who don’t have any symptoms at all, but are selected on the basis of their amyloid positivity,” says Sperling. “And the question will be whether we can prevent the emergence of clinical symptoms. For me this is thrilling.”