Testing a test for Alzheimer disease

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Editorial

Testing a test for Alzheimer disease

Randall J. Bateman, MD; and David Eidelberg, MD

In this issue of *Neurology*, Edison et al.[1] present a study which compares a newly developed amyloid imaging technique (PIB PET) pioneered by Klunk et al.[2] and glucose metabolism (FDG PET) imaging to cognitive testing in Alzheimer disease (AD). They expand the observation that PIB PET is highly sensitive (89%) and specific for clinical AD compared to normal age-matched controls. They demonstrate correlation of recognition memory tests with PIB PET, as well as other memory testing with temporal and hippocampal FDG PET. In addition, they demonstrate that PIB PET imaging correlates with decreased glucose utilization in the temporal and parietal cortex, but not in the frontal cortex. PIB PET is a molecular amyloid imaging technique, and has potential for providing quantitative measures of amyloid in the brain,[3] which previously could only be obtained postmortem. The utility of PIB PET will depend on the questions being asked of the test.

PIB PET may be evaluated for diagnostic purposes, such as in the differential diagnosis of dementia or as a test of amyloid pathology that may predict the onset of clinical disease. In a recent *Neurology* study by Mintun et al.,[4] PIB PET was positive in 9 of 10 participants with very mild or mild AD, and was also positive in 4 of 20 age-matched controls (mean age 77.4 years), which agrees well with pathologic studies of amyloid deposition in this age group. As Mintun et al. suggest, the most exciting use of PIB PET as a diagnostic tool may be as a predictive test to determine who is at risk for developing AD, thus providing a window of opportunity for intervention. Disease-modifying treatments will likely be most effective when given before the onset of clinically evident dementia. However, by the time clinical diagnosis of AD is made, extensive neuronal loss has already occurred,[5] so that identifying the pathologic changes that occur in AD before clinical onset should be the goal. However, until disease-modifying treatments are available for AD, there may be little clinical incentive for a predictive test.

PIB PET may also be tested in clinical research studies of therapies that target amyloid, and may provide a measure to study the effect of proposed disease-modifying treatments on brain amyloid deposition. Biochemical, genetic, and animal model studies implicate amyloid-β (Aβ) as a pathogenic peptide in AD. Multiple lines of evidence suggest that Aβ accumulation and change of conformation to forms with a high β-sheet structure (e.g., amyloid, oligomers) is central in AD pathogenesis.[6] Many pharmaceutical companies now have programs that target Aβ, with several in phase II, and one in phase III clinical trials. Due to the slow progressive clinical course of AD, clinical trials may take several years to determine if any effect of the treatment is seen clinically. Therefore, an important question PET PIB may be able to help resolve is whether the treatment is hitting its target and changing the amount of amyloid present in the brain.

There are a number of ways to assess the effectiveness of treatments, with clinical outcomes being the gold standard. Important information may be obtained by measuring biomarkers in addition to PIB PET. For example, CSF Aβ 42 has been well documented to be lowered in AD and in people at high risk for AD (advanced age and ApoE e4 carriers). A recent study by Fagan et al.[7] demonstrated excellent correlation between low CSF Aβ 42 and positive PIB PET imaging. There is now a wide range of biomarkers that may be used to measure effects of treatments. CSF studies of Aβ, tau, and other proteins may provide measures of effects on protein levels, and labeling proteins during production in vivo may give pharmacodynamic information on treatment effects.[8] Structural MRI provides information on rates of atrophy, such as seen after an active Aβ immunization trial.[9] FDG PET may be useful as a metabolic imaging modality to assess synaptic activity and early studies in functional MRI

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suggest correlations to neuropsychometric performance. Several of these biomarkers are being extensively studied in a large national cooperative effort for AD biomarkers (ADNI).

PIB PET is an exciting imaging modality that measures the biochemical and pathologic distribution of amyloid in the living human brain. How PIB PET is applied depends on the questions that are asked, and the current study gives further support for its applicability in identifying AD. It has an obvious role in basic research, and is potentially useful as a tool in clinical trials. Whether PET imaging with PIB or related radiotracers will be adopted as a diagnostic test for AD will require large controlled studies of AD compared to other dementias with follow-up pathologic confirmation. Until then, PIB PET is increasing our knowledge of amyloid and its relationship to AD.

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