Imaging biomarkers in neurodegenerative diseases

Clifford R. Jack, Jr., M.D.

One way to think about neurodegenerative diseases is to divide them into those that are and those that are not typically associated with dementia. For example, Alzheimer’s disease (AD) is while amyotrophic lateral sclerosis or certain movement disorders are typically not associated with dementia. This talk will focus on neurodegeneration that is associated with dementia in the elderly. There are several neurodegenerative disorders that fall into this category including fronto temporal lobar degeneration and dementia with Lewy bodies. However by far the most common neurodegenerative disorder associated with dementia in the elderly is AD, and that will be the focus of this talk. There are several reasons for this emphasis on AD. The estimated current prevalence of AD in the United States is 4.5 million individuals. The incidence disease doubles every 5 years after age 60 resulting in an estimated prevalence by the year 2050 of 14 million individuals in the US alone. AD is the most common illness leading to nursing home placement. Care for affected individuals currently costs up to 140 billion dollars per year in health care, nursing home, and lost productivity. For the above reasons as well as recent basic advances illuminating the mechanisms underlying AD, the pharmaceutical industry has focused increasingly on this disorder. Consequently, a focus on AD is highly appropriate in a discussion of biomarkers for neurodegenerative disease.

The major pathologic features which characterize AD are senile plaques, neurofibrillary tangles, decreased synaptic density, neuron loss, and cerebral atrophy. Intense debate has centered on which of two primary neuropathologic protein deposits are causative - amyloid plaques vs. neurofibrillary tangles. The anatomic distribution of neurofibrillary tangles is much more closely associated with the pattern of neuron loss and therefore with the clinical symptoms in AD. However, the available genetic evidence strongly implicates a derangement in amyloid metabolism as the primary instigating factor in AD. The known autosomal dominant mutations that lead to inevitable development of early onset AD all are related to abnormal amyloid metabolism. Transgenic mice with these mutations recapitulate amyloid plaques seen in human AD subjects. Consequently most in the field believe that the instigating molecular event(s) in the cascade ultimately leading to AD are related to amyloid dysmetabolism.

The most promising biomarkers of AD can be broken into two categories: (1) abnormal levels of certain proteins found in the cerebro spinal fluid (CSF) and (2) imaging. CSF biomarkers are decreased Aβ$_{1-42}$ (a proteolytic fragment related to abnormal amyloid metabolism) and increased tau (a protein related to neuronal injury). Given the relationship between abnormal protein accumulation and neurodegeneration, imaging biomarkers of AD by definition imply successful detection of microscopic events at a macroscopic level. The most promising imaging biomarkers are PET and MRI based techniques. Historically the most widely studied PET based technique is FDG, which reveals decreased glucose metabolism in a characteristic temporal parietal association cortex distribution.
However, the most important recent development in AD imaging (and perhaps in the AD field overall) is the development of PET based amyloid binding ligands. The most widely studied of these at present is Pittsburgh Compound B (PIB).

MR findings associated with AD are as follows. Structural MRI demonstrates atrophy, which begins in medial temporal limbic areas and then spreads to association neocortex. $^1$HMRs findings are decreased N-acetylaspartate and increased myo-Inositol. Choline findings have been less consistent with some studies reporting increase and others decrease in this metabolite. Diffusion imaging reveals increased apparent diffusion coefficients and decreased fractional anisotropy. Arterial spin labeling reveals decreased perfusion. Functional activation studies reveal decreased activation in more severely impaired subjects while increased activation has been reported in very mildly impaired subjects early in the course of the disease. Finally, resting state studies indicate decreased functional connectivity in the default mode network.

The most widely studied MR technique in AD at present and therefore the most thoroughly tested candidate MR biomarker is structural MRI. Several stages of validation testing have been performed, and these can be divided into the following categories:

1) Cross sectional case-control studies in which the cases are patients with probable AD.
2) Cross sectional case-control studies in which the cases are cognitively normal or mildly impaired individuals who are at elevated risk of developing dementia in the future.
3) Longitudinal cohort studies that test the ability of MR techniques to predict future progression to dementia in cognitively normal or mildly impaired individuals.
4) MRI-pathological correlation studies
5) Longitudinal cohort studies that correlate clinical disease progression over time with change on serial MRI.