Imaging and Biomarkers in Early Alzheimer's Disease and Mild Cognitive Impairment

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A major focus of research on aging and dementia pertains to the prediction of future cognitive decline. Toward this end, several longitudinal studies are under way that are designed to explore early predictors of cognitive impairment. Neuroimaging techniques and biomarkers have shown promise in this application. Ultimately, it is likely that the use of a combination of neuroimaging and chemical biomarkers will be involved in predicting the development of dementia and Alzheimer's disease (AD).

Alzheimer's disease (AD) may be the most vexing problem facing many parts of the world as populations age. Many other chronic diseases associated with aging are showing a slowing of progression as effective therapies are developed. However, no therapies are available for AD that alter the underlying disease process; therefore, the prevalence of the disease continues to increase.[1,2] Estimates from the Alzheimer's Association suggest that, in the United States alone, there are ~5.3 million people with AD, and the figures on a worldwide basis for dementia are estimated to be 20–30 million.

Although there are currently no disease-modifying therapies for AD, more than 100 compounds are in various phases of development by pharmaceutical companies. A challenge in the development of new therapies for AD stems from the uncertainty of the underlying diagnosis. AD can be identified quite accurately in its midstages by most clinicians, but in the earlier phases of the disease process, a precise diagnosis can be elusive. The American Academy of Neurology, in an evidence-based medicine review of the literature on dementia and AD, concluded that clinicians are fairly accurate in their diagnoses at later stages of the disease, as is demonstrated when the clinical diagnosis is compared with autopsy findings.[3] However, when the clinical signs are mild, and there is a more variable expression of the clinical features, there is less certainty with regard to the diagnosis.

In the past decade, the condition known as mild cognitive impairment (MCI) has come to represent a syndrome with early features of what might evolve into clinical AD.[4] MCI refers to the clinical condition in which subjects are usually only mildly impaired in memory, with relative preservation of other cognitive domains and functional activities, and they do not meet the criteria for dementia. This entity has stimulated a great deal of research on the prodromal stages of what could become fully developed clinical AD.[5] However, as clinicians increasingly make the diagnosis on the basis of subtle features of the syndrome, they gain sensitivity in picking up early cases but sacrifice specificity with respect to the precise outcome of the early prodromal condition. This has become evident with the recent reports of randomized clinical trials designed to develop treatments for MCI.[6,7] The annual progression rate from MCI to AD varied greatly in these trials, from 5–6% per year to 16% per year. Some of this variability was due to the design of the studies, but other features, such as lack of specificity of clinical criteria, played a role.

As research data on MCI have accumulated, it has become apparent that the specificity of the clinical outcome can be enhanced through using neuroimaging and biomarkers.[8,9] As a result of this growing literature, a large study in the United States—the Alzheimer's Disease Neuroimaging Initiative (ADNI)—was set up to address some of these issues.[10,11] In parallel, comparable efforts in Japan (J-ADNI) and Europe (E-ADNI) have been developed, as well as a counterpart study in Australia, and there is increasing expectation that the data from these studies will complement one another. These results will allow for the prediction of outcomes for persons with MCI and, ideally, eventually even for asymptomatic persons who are at risk for developing AD and other dementias.

In recent years, there has been an evolving theoretical framework postulating that the AD process likely begins years, if not decades, prior to the development of clinical symptoms—even those of the MCI stage.[12] Although the precise temporal relationship among the various pathologic entities involved in AD is not certain, many investigators believe that the deposition of the Aβ peptide may be the initiating event (**Figure 1**). Currently, Aβ deposition can be inferred by testing the cerebrospinal fluid

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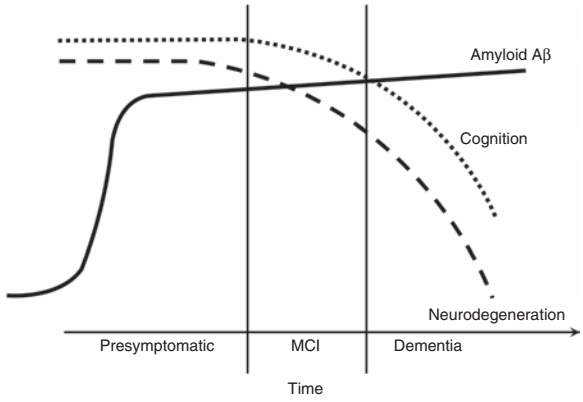

Figure 1 Theoretical time course of amyloid deposition relative to subsequent neurodegeneration and cognitive decline. MCI, mild cognitive impairment.

(CSF) and/or through amyloid imaging techniques.[9,13] Following the deposition of Aβ, there may be a rise in the expression of certain species of tau proteins—particularly total tau and the hyperphosphorylated form (p-tau)—and a decrease in synaptic integrity as indexed by fluorodeoxyglucose positron emission tomography (FDG PET).[14] Subsequently, evidence of neuronal damage may become manifest through the development of atrophy of certain structures such as the hippocampus and entorhinal cortex, as imaged by magnetic resonance imaging (MRI). Following this cascade of events, or at some point during their development, changes in cognition appear. If this scenario is partly accurate, then imaging and chemical biomarkers may become the mainstay in the identification of individuals who are likely to develop the clinical syndrome we now call AD. Against this background, what is the evidence for this putative constellation of events?

NEUROIMAGING

Among the many neuroimaging techniques available (**Figure 2**), structural MRI has generated the most data. It is commonly recognized that atrophy, particularly of medial temporal lobe structures such as the hippocampus and the entorhinal cortex, develops early in the disease process.[15] In addition, measurements of whole-brain atrophy such as those demonstrated through use of the boundary shift integral technique or other indexes of ventricular expansion provide additional support for their utility.[16] Numerous studies have demonstrated that these measurements are quite useful in predicting clinical progression from MCI to AD, and data from the ADNI support this.[8] As a result of these data, projected sample sizes for the conduct of clinical trials can be dramatically reduced, given the tight variance surrounding these neuroimaging measurements. Structural MRI measurements have therefore become the gold standard in imaging in aging and dementia.

There is a growing body of data indicating that functional evaluations such as those provided by FDG PET and MRI spectroscopy also provide additional information on the state of neuronal and synaptic function.[17,18] These findings can be closely aligned with cognitive function and the progression of the clinical state.[19,20] As the resolution of these techniques improves,

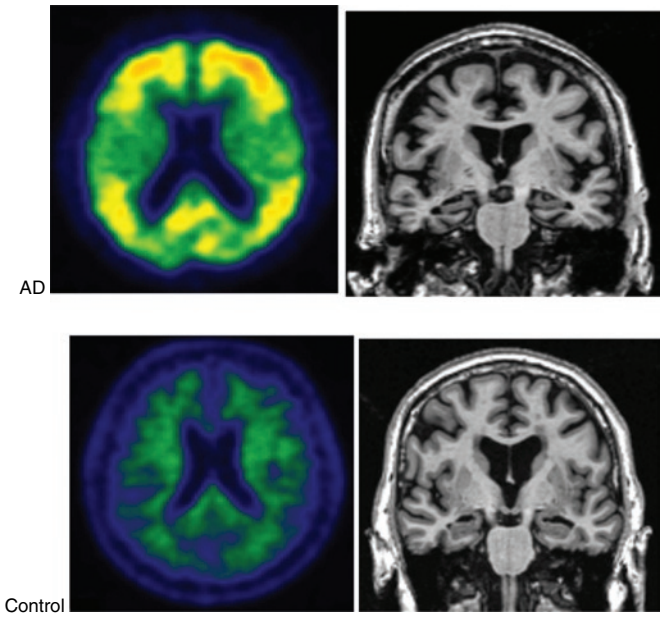

Figure 2 ^{11}C Pittsburgh compound B (PiB) scans (left) and magnetic resonance imaging (MRI) scans in a subject with Alzheimer's disease (AD) and a healthy control subject. The ^{11}C PiB scan shows amyloid tracer retention in the red and yellow areas for the subject with AD and no tracer retention in the control subject. The MRI scan in the subject with AD shows generalized atrophy with more focal accentuation in the hippocampus. The MRI scan in the control subject shows age-related changes.

they can be considered important adjuncts in characterizing incipient disease. There is also a growing body of literature suggesting that functional MRI may be useful in this context.[21] These additional findings have been shown to be particularly informative in the case of individuals who may be genetically predisposed to develop AD because they have one or more apolipoprotein E4 alleles.[22]

More recently, the advent of molecular imaging has opened a new window to the development of the pathology of AD. Tracers have been developed that allow for the identification of amyloid deposition in the brain *in vivo*.[23] Most of the research to date has pertained to ^{11}C Pittsburgh compound B, which enables investigators to study the presence or absence of amyloid pathology not only during the developmental stages of the disease process but also during the course of its evolution.[24] The techniques provide powerful new tools for imaging the underlying disease pathology as it progresses over time.

BIOMARKERS

In concert with the growing research on neuroimaging, there has been an increase in the availability of data on the role of chemical biomarkers in the diagnosis of AD and in the identification of subjects in the MCI stage who are likely to develop AD.[9] Although there have been several studies on the ability of CSF biomarkers to differentiate normal subjects from those with AD,[25–27] only recently have studies on MCI suggested that subjects who fulfill the clinical criteria for amnestic MCI, and who possess the CSF profile characteristic of AD, will progress more rapidly toward developing the disease.[28] The ADNI

recently demonstrated the utility of this profile, suggesting that these biomarkers may be useful in the selection of MCI subjects for clinical trials involving drugs with disease-modifying characteristics.[13]

There is also evidence from several studies that CSF biomarkers may be useful in predicting which asymptomatic normal subjects may be at risk for developing MCI and dementia in the future.[29] In effect, the neuroimaging and biomarker profile may be able to characterize persons at risk of AD and dementia prior to the development of clinical symptoms.

COMBINATIONS OF MARKERS

In all likelihood however, considering the mounting quantities of data from all the sources described, the final predictors of clinical progression will be the findings from a combination of the above techniques. That is to say, depending on the stage of disease progression, a combination of imaging and biomarkers will likely contribute to the best prediction model. Recent data suggest that this approach is already bearing fruit. A recent study suggested that even though amyloid may be deposited in the brain, this may not be sufficient to predict the outcome in an individual patient.[30] However, the subsequent course of the disease may be best depicted by an evaluation of neuronal integrity, in this case by using structural MRI, to yield dynamic information. It is likely that other evaluations, such as those using FDG PET and perhaps CSF-tau and p-tau, may give additional information on the time course of the progression, once the amyloid substrate has been established. In other words, the presence of amyloid in the brain sets the stage for subsequent events, but the temporal course over which those events develop may be better predicted by other imaging and biomarker measurements.

If this scenario approximates reality, it is likely to have implications for the development of therapies. In other words, depending on the point in the continuum of disease progression, certain imaging and chemical biomarkers may be more or less informative. For example, if one were investigating a secondary prevention therapy at the MCI stage, then perhaps a combination of an amyloid marker, imaging, and CSF might be useful, along with an index of neuronal change such as quantitative MRI. These measurements would be most informative at this point in the spectrum. Alternatively, if one were studying primary prevention therapies, an early amyloid deposition marker such as imaging or CSF might be adequate because some of the neuronal and synaptic markers may not be informative at that point in the spectrum. All of this is theoretical at this point in time and subject to further investigation, and the final utility of these evaluations remains to be demonstrated. The evidence cited above for functional imaging might suggest that FDG PET can be informative early in the course of the disease, especially in ApoE4 carriers.[22]

SUMMARY

In summary, the interplay of clinical analyses, neuroimaging, and biomarkers poses exciting new challenges in the characterization of the course of cognitive disorders such as AD. It is likely that these measures will be validated and sorted out over time with respect to their relative utility. Several of the investigations discussed probably provide redundant information, and those that are more expensive or invasive will be eliminated. In asymptomatic individuals, consideration will need to be given to the sequential utility of various measures. It would be impractical to carry out amyloid imaging scans or spinal taps on the general population. However, if less expensive, safer, and less invasive techniques could be developed that would provide information allowing us to stratify groups of individuals into variable risk levels, then the more expensive and invasive measures could be introduced sequentially as the circumstances suggest. All this work is progressing at a rapid pace, and as soon as disease-modifying therapies are developed, it will take on a new sense of importance and urgency.

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CONFLICT OF INTEREST

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