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

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Abstract

A major focus of research on aging and dementia pertains to the prediction of a future cognitive decline. Toward this end, several longitudinal studies are currently underway designed to explore early predictors of cognitive impairment. Neuroimaging measures and biomarkers have been shown to be promising in this capacity. Ultimately, it is likely that a combination of neuroimaging and chemical biomarkers will be involved in predicting future dementia and Alzheimer's disease.

Keywords

Alzheimer's disease; neuroimaging; biomarkers; mild cognitive impairment

Alzheimer's disease (AD) may be the most vexing problem facing societies as the world populations age. Many other chronic diseases associated with aging are showing a slowing of progression as effective therapies are developed (www.alzstudygroup.org). However, there are no therapies available for AD that alter the underlying disease process, and as such, the prevalence continues to increase.[1, 2] Estimates from the Alzheimer's Association suggest that, in the U.S. alone, there are approximately 5.3 million persons with AD, and the figures on a worldwide basis for dementia are estimated to be 20–30 M.

While there currently are no disease-modifying therapies for AD, over 100 compounds are in various phases of development by many pharmaceutical companies. A challenge in the development of new therapies for AD stems from the uncertainty of the underlying diagnosis. Alzheimer's disease can be identified quite accurately in its mid-stages 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 quite accurate in the later stages of the disease when the clinical diagnosis is compared to autopsy confirmation.[3] However,

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when the clinical signs are mild and there is a more variable expression of the clinical features and less certainty in the diagnosis.

In the past decade, the condition is known as mild cognitive impairment (MCI) has come to represent a syndrome with only early features of what might evolve into clinical AD.[4] Mild cognitive impairment 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 criteria for dementia. This entity has stimulated a great deal of research on the prodromal stages of what will become fully developed clinical AD.[5] However, as clinicians make the diagnosis with increasingly subtle features of the syndrome, they gain sensitivity at 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 Alzheimer's disease 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 concerning the clinical criteria, played a role.

As research on MCI has accumulated, it has become apparent that the specificity of the clinical outcome can be enhanced 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 developed to address some of these issues.[10, 11] In parallel, comparable efforts in Japan (J-ADNI), Europe (E-ADNI) and a counterpart study in Australia have been developed, and there is increasing expectation that these studies will complement each other. These results will allow for the prediction of outcomes of persons with MCI and, ideally, eventually, even asymptomatic persons who are at risk for developing AD and other dementias.

In recent years, there has been an evolving theoretical framework that the AD process likely begins years, if not decades, prior to the development of clinical symptoms, even at the MCI stage.[12] While 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 in the cerebrospinal fluid (CSF) and/or through amyloid imaging techniques.[13][9] 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 an index of a decrease in synaptic integrity as indexed by FDG PET.[14] Subsequently, evidence of neuronal damage may become manifest through the development of atrophy of certain structures such as the hippocampus and enterorhinal cortex as imaged on MRI. Following this cascade of events or at some point during their development, cognitive changes appear. If this scenario is partly accurate, then imaging and chemical biomarkers may become the mainstay in predicting which individuals are likely to develop the clinical syndrome we now call AD. So, 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 enterorhinal cortex develops early in the disease process.[15] In addition, measures of whole brain atrophy such as those demonstrated through use of the boundary shift integral technique or other indices of ventricular expansion provide additional support for their utility.[16] Numerous studies have demonstrated that these measures 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 due to the tight variance surrounding these neuroimaging measures. As such, structural MRI measurements have become the gold standard in imaging in aging and dementia.

There is a growing body of data indicating that functional measures such as FDG PET and MRI spectroscopy also provide additional information on the state of neuronal and synaptic function.[17, 18] These measures can be closely aligned with cognitive function, and the progression of the clinical state.[19, 20] As the resolution of these techniques improve, they can be considered as important adjuncts in characterizing incipient disease. There is also a growing body of literature suggesting that functional MRI may be useful.[21] These measures have been shown to be particularly informative in individuals who may be genetically predisposed to developed AD by virtue of possession of one or more ApoE4 alleles.[22]

More recently, the advent of molecular imaging has opened a new window into 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 11C Pittsburgh Compound B (PiB) which enables investigators to not only study the presence or absence of amyloid pathology during the developmental stages of the disease process, but also the course of the 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 the increase in the data developing on the role of chemical biomarkers in diagnosing AD and in predicting who is going to develop AD from the MCI stage.[9] While 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 those subjects who fulfill the clinical criteria for amnestic MCI, and who possess the CSF profile characteristic of AD will progress more rapidly.[28] The ADNI recently demonstrated the utility of this profile suggesting that in subjects who fulfill MCI clinical criteria these biomarkers may be useful for selection of subjects for clinical trials on drugs with disease-modifying characteristics.[13]

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

Combinations of Markers

In all likelihood however, considering the mounting data from the sources described above, the final predictors of clinical progression will represent a combination of the above techniques. That is, 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 prospect is already bearing fruit. A recent study suggested that as amyloid is deposited in the brain as demonstrated by amyloid imaging, the outcome of the individual is uncertain.[30] However, the subsequent course could be best depicted by a measure of neuronal integrity, in this case, structural MRI yielding a dynamic information about the subsequent disease course. It is likely that other measures such as 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 measures.

If this scenario approximates reality, then it is likely to have implications for the development of therapies. That is, 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 or CSF, might be useful along with an index of neuronal change like quantitative MRI. These measures 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 and subsequent to investigation, and the final utility of these measures remains to be demonstrated. Evidence cited above for functional imaging might suggest that FDG PET may be informative early in the course especially in ApoE4 carriers.[22]

Summary

In summary, the interplay of clinical, neuroimaging and biomarkers poses exciting new challenges in characterizing 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 measures discussed likely 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 do amyloid imaging scans or spinal taps on the general population. However, if relatively less expensive, safe and less invasive measures could be developed and provide information that would allow us to stratify groups of individuals into those at variable risk levels, then the more expensive and invasive measures could be introduced sequentially and the circumstances suggest. While all of this work is progressing at a rapid pace, as soon as disease modifying therapies are developed, this work will take on a new sense of importance and urgency.

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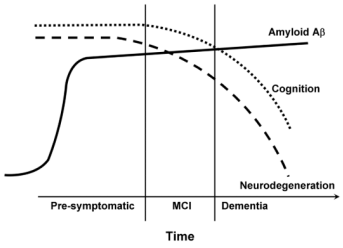

Figure 1.
Theoretical time course of amyloid deposition relative to subsequent neurodegeneration and cognitive decline.

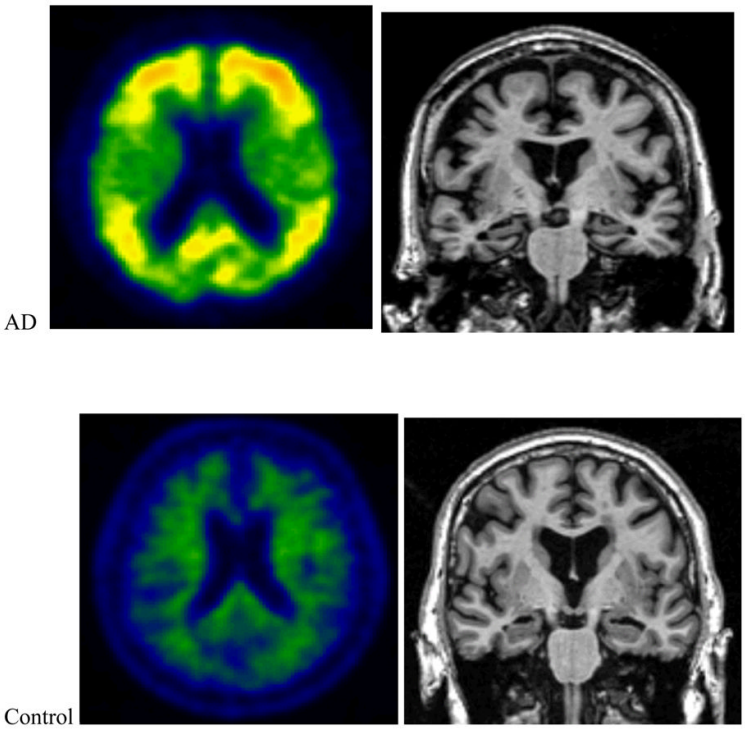

Figure 2.
^{11}C PiB scan and MRI scans for an AD subject and a healthy control subject. The ^{11}C PiB scan shows amyloid tracer retention in the red and yellow areas and no tracer retention in the control subject. The MRI scan for the AD subject shows generalized atrophy with more focal accentuation in the hippocampus. The MRI scan for the control subject shows age related changes.