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Commentary on “Diagnosis of Alzheimer’s disease: Two decades of progress.” Central role of technology in the treatment and prevention of Alzheimer’s disease

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In his review of 2 decades of progress since his seminal editorial concerning the diagnosis of Alzheimer’s disease (AD), Dr. Khachaturian wrote: “The early pioneers of the field were able to make some groundbreaking observations about dementia because of access to a wealth of new technologies for studying the brain.”

The technologies to which Dr. Khachaturian refers were primarily “advances in histology (chemistry of tissue stains), light microscopy, neuroanatomy, and other areas of biology.” During the past 2 decades, other technologies have also been developed that are having a growing impact on diagnosis, monitoring of progression, and early detection. These technologies can be grouped roughly into imaging and biomarker technology. It can be expected that the major advances in the field will come from applications of these technologies to the problems of Alzheimer’s disease.

The biomarker field is already vast and beyond the ability of this author to describe comprehensively. There has been huge interest in blood and cerebrospinal fluid (CSF) measurements of β -amyloid and τ , in their various forms. More recently, there has been growing interest in isoprostanes and other potential markers of injury and inflammation. The fields of proteomics, metabolomics, and genomics are just beginning to be exploited for studies of dementia. Biomarkers of inflammation (C-reactive protein, tumor necrosis factor, interleukin) and metabolism (insulin degrading enzyme, leptin, growth hormone, cortisol, dihydroepiandrosterone, and other steroids) have been reported in association with aging and cognitive decline. Intensive investigation continues to identify genes associated with Alzheimer’s disease, and other studies will explore genetic markers associated with Alzheimer’s subtypes, and rate of progression.

Although advances in pathologic analysis of brain tissue continue (with improved histology, electron microscopy, and immunofluorescence), advances in neuroimaging have opened up an entirely new approach to studying changes in the brain associated with Alzheimer’s disease. Neuroimaging can be classified largely into x-ray, computed tomography (CT), position emission tomography (PET), single photon emission tomography (SPECT), and magnetic resonance imaging (MRI).

CT scanning is probably the imaging technique most used to evaluate individuals with cognitive decline and dementia because it is inexpensive, fast, and able to detect brain tumors, subdural hematomas, and large strokes. Therefore, it is an appropriate, inexpensive imaging technique to rule out anatomic causes of cognitive impairment. Currently, CT lacks the soft tissue contrast of MRI, and is not used as a functional imaging technique; therefore, CT lacks the capability to help “rule in” AD. Consequently, there is very little research underway using CT in the Alzheimer’s field.

Both PET and MRI were developed in the early to middle 1970s, and have enjoyed growing popularity for diagnostic assessment and research. These techniques greatly benefit from technological developments in physics, engineering, computer science, and the new field of image processing (which include bioengineers, electrical engineer's, mathematicians, statisticians, and computer scientists).

PET scanning visualizes uptake of radioactive tracers in the brain. Although some PET work on AD has been done quantifying cerebral blood flow and receptor-specific markers, the majority of PET studies have used fludeoxyglucose (FDG), which is taken up by the glucose transporter and reflects the brain's metabolic rate of glucose consumption. Many investigators have shown that AD is characterized by reduced FDG uptake in the temporal parietal cortex, especially the posterior cingulate gyrus and the medial temporal lobe. Furthermore, subjects with mild cognitive impairment (MCI) who are at high risk for AD have a similar pattern of metabolic impairment. Interestingly, normal subjects who are not impaired who have an *APOE* ϵ 4 allele show similar changes, including *APOE* ϵ 4 allele subjects in their 20s. Other recent studies have reported that FDG PET reductions help predict future cognitive decline in normal elderly.

Perhaps the most exciting developments in neuroimaging of AD in recent years have been the development of PET tracers for brain amyloid, including F19 2-dialkylamino-6-acylmalononitrile substituted naphthalenes (DDNP) and the C11 Pittsburgh compound (PIB). DDNP has also been shown to highlight involved areas in frontotemporal dementia, suggesting that this marker is not highly specific for amyloid, whereas PIB seems relatively specific. At this time, it is much too early to predict the impact of these compounds on treatment trials and diagnosis, especially because some normal elderly are found to have heavy amyloid deposits at autopsy. Nevertheless, one potential use of brain amyloid imaging may be to monitor the effects of treatments aimed at reducing brain amyloid.

MRI (in the interests of full disclosure, this author works primarily with MRI/MRS) uses magnetic fields and radio-waves to image brain structure, function, and metabolism non-invasively without isotopes or ionizing radiation. MRI is capable of high resolution (below 1 mm) and has the most outstanding soft tissue contrast of any brain imaging technique. MRI can visualize the gray matter, white matter, cerebrospinal fluid, tumors, strokes, and white matter disease (sometimes called white matter lesions, leukoariosis, or unknown bright objects). Diffusion-weighted MRI has high sensitivity to detect acute stroke. Diffusion tensor MRI is able to identify white matter fiber tracts. Perfusion MRI can quantitatively measure cerebral blood flow in gray and white matter, providing information roughly equivalent to FDG PET. Susceptibility-weighted MRI detects accumulation of iron in the brain. MR spectroscopy detects a variety of brain metabolites including *N* Acetyl aspartate (a neuronal marker), myo-inositol (a glial marker), choline compounds, creatine, glutamate, glutamine, and gamma aminobutyric acid. MR spectroscopic imaging displays these metabolites as an image.

During the past 20 years there has been growing interest in the use of MRI for diagnostic evaluation, monitoring of progression, and early detection. Some physicians use MRI for initial evaluation of cognitive impairment, because it detects anatomical causes of cognitive impairment (similar to CT, but more expensive) while also detecting hippocampal atrophy, a marker of AD. However, vascular dementia and frontotemporal dementia are also associated with hippocampal atrophy; this feature is not at all specific for AD. There has been growing interest in longitudinal MRI measurements of brain atrophy as a measure of progression of neurodegeneration. Others have shown changes in AD using MRS, perfusion MRI, and diffusion-tensor imaging, but the role of these modalities in diagnosis, monitoring of therapy, and early detection, remains to be determined with more research.

Obviously, everyone's goal is to see an effective treatment developed that will slow the progression of AD. Once identified, such a treatment would be used to slow conversion from MCI to AD and then used in a primary prevention trial. Many pharmaceutical companies, biotech companies, and the NIH are together spending billions of dollars in this quest. One big problem is: how does one quickly, efficiently, and inexpensively demonstrate that a treatment is slowing the progression of AD? Because neuropsychological tests for cognition and measures of activities of daily living have so much variability, the answer is to identify a "validated biomarker" for AD. The major candidates for such a biomarker are MRI, PET, and blood and CSF biomarkers. However, the current data on these markers come from many laboratories, using many methods, on different subjects. To determine which of these many candidates will provide the best marker of progression, the National Institutes of Aging (as well as NIBIB), together with the pharmaceutical industry (through the Foundation for NIH) has funded the Alzheimer's Disease Neuroimaging Initiative [1]. This is a longitudinal MRI, PET, and biomarker study of 400 MCI, 200 AD, and 200 controls in 60 centers around the United States and Canada. The biomarker data will be validated by correlation with extensive clinical and neuropsychological data. All of the data and raw and processed images are available to the public on the Worldwide Web as the data are collected.

Without question, the need for effective treatments is greatly underscored by the rapid growth of the elderly, where the prevalence of AD approaches 50% in those older than 90. Furthermore, in the past, diseases of the elderly were most widely seen in the "western countries." By economic and technical advances, China and India are leading a growing elderly population in Asia. A sobering note reminds us that most AD treatment research is focusing on reducing β -amyloid in the brain. If β -amyloid is not a primary cause of neurodegeneration (and simply an epiphenomenon), we will re-experience the problems in the field of cancer, where new treatments of solid tumors, such as immunotherapy, tumor necrosis factor, and anti-angiogenesis therapy have been disappointing, to the say the least. But notwithstanding the problems, the diagnosis, monitoring of progression, and early detection of AD are greatly facilitated with advanced analytical methods of biological fluids, MRI, and PET. All of this work is supported greatly by the huge advances in computer technology for image reconstruction, databasing, and data transfer through the Internet. To paraphrase the first 3 rules of real estate, the message of this Commentary is technology, technology, technology.

References

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