EDITORIAL

EDITORIAL

IMAGING AND BIOMARKERS WILL BE USED FOR DETECTION
AND MONITORING PROGRESSION OF EARLY ALZHEIMER'S DISEASE

M.W. WEINER

Director, Center for Imaging of Neurodegenerative Disease, VA Medical Center, Professor of Medicine, Radiology, Psychiatry, and Neurology, University of California, San Francisco, U.S.A. Principal Investigator: Alzheimer's Disease Neuroimaging Initiative

During the early development of medicine, clinical diagnosis relied on symptoms, history, as well as the visual, auditory, tactile, and olfactory skills of the physician. More recently, advances of technology led to the development of the stethoscope, EKG machine, X-ray, etc. Another line of technology involved measurements of electrolytes and other substances in blood, urine and other body fluids. Most areas of medicine have greatly benefited from these advances especially in recent decades.

In addition to the clinical diagnostic use of imaging and laboratory tests on body fluids, these same types of measurements have been used in epidemiological studies, for assessment of risk, early detection of disease, leading to the development of risk prevention trials. A prominent example is cardiovascular disease. Even as clinicians argued how myocardial infarctions should be diagnosed (e.g. how much to rely on symptoms, EKG, serum enzymes) a half century of work demonstrated that hypertension and hyperlipidemia were risk factors for subsequent vessel disease. Treatment trials aimed at correction of biomarkers such as hyperlipidemia ultimately demonstrated the value of reducing cardiovascular risk factors. Many other examples of how medicine uses technology for early disease detection include use of the Prostatic Specific Antigen for prostate cancer and mammography to detect breast cancer. In each of these examples, there was always considerable debate concerning whether the biomarker (e.g. an imaging measurement, or laboratory test) provided a "valid" measurement of the disease process. Ultimately, validation required correlation between the biomarker and the ultimate clinical diagnosis and autopsy confirmation. Concerning treatment, validation meant that a treatment which affected the biomarker (e.g. by reducing lipid levels or blood pressure) ultimately had a beneficial clinical outcome (reduction of strokes and heart attacks).

For a variety of reasons (e.g. the brain being surrounded by the skull, brain function not easily quantified by technological measurements) the assessment of brain disorders has largely relied on traditional methods of assessing behavior and cognition. Early uses of technology to detect brain disorders included EEG, measurement of cerebral spinal fluid and brain imaging with X-Ray CT and MRI. However, even today most clinicians use imaging to "rule out" other causes of dementia,

and the diagnosis of Alzheimer's disease primarily uses clinical information. Fortunately, this situation is now undergoing rapid evolution.

There are a number of candidate biomarkers which can be used for diagnosis, early detection, or monitoring progression of Alzheimer's disease. Structural MRI demonstrates hippocampal atrophy in demented and mildly impaired subjects. Fludeoxyglucose PET shows reduced glucose metabolism in the posterior cingulate gyrus and hippocampal regions. Recent studies with C-11 PIB and F18 amyloid ligands suggest that the brain amyloid load may be quantified. As expected, subjects with Alzheimer's almost all have high amyloid loads detected by such imaging techniques. A high fraction of MCI and a lower fraction of normal elderly also have high brain amyloid. Measurements of CSF obtained by lumbar puncture show that patient's with Alzheimer's disease have low CSF amyloid and elevated tau and phosphotau. A variety of proteins and other substances in blood also appear to change in Alzheimer's disease.

For many years it's been known that many elderly subjects who appear cognitively normal for age, have evidence of Alzheimer's pathology at autopsy. An important question is: do normal elderly subjects with evidence for Alzheimer's pathology (e.g. small hippocampus, reduced posterior cingulate glucose metabolism, reduced CSF amyloid and elevated tau etc) have a higher risk for cognitive decline and ultimate conversion to dementia? Similarly, do subjects with MCI who have biomarker/imaging evidence for Alzheimer's pathology have a higher risk for future conversion to dementia?

This special (1-17) issue focuses on the use of various imaging techniques and biomarkers for Alzheimer's disease clinical trials. In this setting imaging/biomarkers have at least 4 uses:

- 1) As markers of progression. In this case, it is expected that a treatment which slows the rate of progression, would slow the rate of change of the biomarker. Brain atrophy, especially in the hippocampal region, is generally thought to be a good progression marker.

- 2) To stratify subjects into "groups" especially to identify AD pathology. There are a number of candidates for this use including: hippocampal or total brain volume, FDG PET uptake, amyloid imaging, and CSF amyloid and tau

3) As "predictors" of future decline and conversion to AD (the same as mentioned previously). These predictors, when used as baseline covariates, can be used to improve power in trials

4) To identify Alzheimer's pathology in normal elders or those with mild complaints or cognitive impairments. The same aforementioned markers are candidates.

The various papers in this special issue all deal with one or another use of such imaging/biomarkers for clinical Alzheimer's trials (1-17)

Ultimately as prevention treatments are worked out, imaging/biomarkers will be used to identify people at risk and also as progression markers/ The ultimately validation will be achieved by following subjects to conversion (to MCI or dementia) and finally pathological validation with autopsy. Ultimately, early intervention trials will be performed on normal elderly subjects, or subjects with mild cognitive complaints, using imaging/biomarkers to select subjects at high risk for AD pathology, and as outcome measures to detect treatment effects. The value of the biomarkers will be validated by following such subjects long term to determine cognitive decline, conversion to dementia, and pathological confirmation at autopsy. This is the path to the prevention of Alzheimer's disease.

References

1. S. Lovestone, M. Thambisetty. Biomarkers for Alzheimer's Disease Trials – Biomarkers for What ? A Discussion Paper. *J Nutr Health Aging*. 2009; 13(4):334-336
2. P.S. Aisen. Interpreting Biomarker Data in Therapeutic Trials. *J Nutr Health Aging*. 2009; 13(4):337-338
3. C. Sampaio. Biomarkers in Clinical Trials of Alzheimer Disease (AD): What Is Expected from Regulatory Agencies? *J Nutr Health Aging*. 2009; 13(4):339-340
4. E.R. Siemers. How Can We Recognize "Disease Modification" Effects? *J Nutr Health Aging*. 2009; 13(4):341-343
5. P.J. Visser. Use of Biomarkers To Select The Target Population For Clinical Trials in Subjects with Mild Cognitive Impairment. *J Nutr Health Aging*. 2009; 13(4):344-345
6. A. Nordberg. Molecular Imaging Markers in Clinical Trials in Alzheimer's Disease. *J Nutr Health Aging*. 2009; 13(4):346-347
7. G.B. Frisoni. Neuro-Imaging: Structural And Functional Imaging. *J Nutr Health Aging*. 2009; 13(4):348-349
8. N.C. Fox, J. Kennedy. Structural Imaging Markers for Therapeutic Trials in Alzheimer's Disease. *J Nutr Health Aging*. 2009; 13(4):350-352
9. W.M. van Der Flier, P. Scheltens. Knowing the Natural Course of Biomarkers in AD: Longitudinal MRI, CSF and PET Data. *J Nutr Health Aging*. 2009; 13(4):353-355
10. B. Dubois. Interest of the New Criteria for Drug Trials in AD. *J Nutr Health Aging*. 2009; 13(4):356-357
11. K. Blennow, H. Zetterberg. Use of CSF Biomarkers in Alzheimer's Disease Clinical Trials. *J Nutr Health Aging*. 2009; 13(4):358-361
12. S.B. Hendrix, G.K. Wilcock. What We Have Learned from the Myriad Trials. *J Nutr Health Aging*. 2009; 13(4):362-364
13. P. Douillet, J.-M. Orgogozo. What We Have Learned from the Xaliproden Sanofi-Aventis Trials. *J Nutr Health Aging*. 2009; 13(4):365-366
14. C. Wischik, R. Staff. Challenges in the Conduct of Disease-Modifying Trials in AD: Practical Experience from a Phase 2 Trial of Tau-Aggregation Inhibitor Therapy. *J Nutr Health Aging*. 2009; 13(4):367-369
15. D. Saumier, P.S. Aisen, S. Gauthier, B. Vellas, S.H. Ferris, A. Duong, J. Suhy, J. Oh, W. Lau, D. Garceau, D. Haine, J. Sampalis. Lessons Learned in the Use of Volumetric MRI in Therapeutic Trials in Alzheimer's Disease: The ALZHEMEDTM (Tramiprosate) Experience. *J Nutr Health Aging*. 2009; 13(4):370-372
16. H. Hampel, K. Broich. Enrichment of MCI and Early Alzheimer's Disease Treatment Trials Using Neurochemical & Imaging Candidate Biomarkers. *J Nutr Health Aging*. 2009; 13(4):373-375
17. C.C. Gispen-de Wied, M. Kritsidima, A.J.A. Elferink. The Validity of Biomarkers as Surrogate Endpoints in Alzheimer's Disease by Means of the Quantitative Surrogate Validation Level of Evidence Scheme (QSVLES). *J Nutr Health Aging*. 2009; 13(4):376-387