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Advancements in Biomarkers for Alzheimer's Disease – The Search for Early Diagnosis and Improved Treatment



Hans J. Moebius, MD, PhD
Senior Vice President, CNS
INC Research

It is estimated that 24.3 million people have dementia today, with 4.6 million new cases of dementia diagnosed every year on a global basis. The number of people affected will double every 20 years to 81.1 million by 2040 (Ferri C et al., 2005). By the year 2020, it is estimated that more than 30% of the US population will be 65 years and older. With age being the single most striking risk factor for Alzheimer's Disease (AD), the search for both early diagnosis and much improved treatments is ever increasing.

Yet clinical diagnosis of AD is inaccurate about 10% to 15% of the time - even among experienced investigators. Biomarkers might serve to improve the accuracy of diagnosis (Thal et al., 2006) as well as improve the average 50% or less efficacy of currently available one-pill-fits-all drugs. Thus, we've seen the importance of biomarkers of AD growing steadily in the past decade with the search for AD biomarkers and the biomarker market as a whole (CNS, cancer, diabetes, obesity, etc.) expected to multiply at least six fold in the next 5 years (Business Insights Report 2008).

Although there is currently no laboratory test to confirm AD, several promising avenues of biologic markers are being pursued. Drug researchers should be aware of the current progress of AD biomarkers and how they may affect their development process – from a scientific and regulatory perspective.

Today, the clinical diagnosis of AD is based on identifying elements within the patient's history and clinical exam that are suggestive of AD together with exclusion of other causes of dementia derived from brain imaging or laboratory tests. The two most commonly used criteria for the diagnosis of AD are based on:

- 1) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. The DSM-IV criteria requires an insidious onset with continuing decline of cognitive function that results in impairment of social and occupational function. They also require memory impairment and at least one other cognitive deficit that cannot be explained by other psychiatric, neurological, or systemic disease.
- 2) National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) joint task force in 1984 (McKhann et al.). They developed criteria that is more detailed and classify AD into definite, probable, and possible levels of diagnostic certainty.

"Biomarking" patients, e.g. by genotyping, has emerged as a tool that could lead to personalized medicine by characterizing AD and potentially treating responses at the DNA, RNA, protein, or metabolite level. Such a biomarker also bears the potential to motivate patient compliance for a therapy that otherwise does not allow the patient to monitor its impact immediately (compare to e.g. statin therapy in hypercholesterinemia).

Obviously, this diagnostic approach requires an individual with subjective complaints or some reported symptoms in the first place. An objective, biologically-based marker suitable and validated to predict risk, diagnose early, stage, and monitor the course and treatment of ("silent") neurodegeneration in AD would represent clear disease progression. Provided it measures a unique feature of AD, it should be sensitive and specific, substituting for a clinically meaningful result. As a surrogate endpoint in clinical AD trials, this convergence of diagnostic, staging and monitoring has the potential to speed up clinical AD development considerably.

It is of particular note for the development of putative disease-modifying drugs for AD that biomarkers might serve as staging instruments also at pre-symptomatic stages. In addition, sample sizes of clinical trials might be reduced due to better defined trial populations, and a change in

biomarker scores could be considered supporting evidence of disease modification. Imaging biomarker development includes 1) volumetric magnetic resonance imaging (e.g. hippocampal and entorhinal cortical atrophy) and 2) positron emission tomography assessing either glucose utilization or ligands binding to amyloid plaque (e.g. PIB).

The routine utility of structural brain imaging is limited to the exclusion of other etiologies, as the common features of AD are cortical atrophy and ventricular enlargement, which are neither sensitive nor specific markers of AD and often accompany normal aging. Because no laboratory test currently exists that can diagnose AD during life, laboratory testing is used to exclude alternate etiologies of dementia, especially reversible or treatable causes.

Several encouraging avenues of biologic markers being investigated are related to the histopathologic hallmarks of AD, neuritic plaques and the neurofibrillary tangles. There is general consensus that A β ₁₋₄₂ the important constituent of the neuritic plaques, is significantly reduced in the cerebrospinal fluid (CSF) of AD patients compared with normal older adult controls. CSF tau, on the other hand, the important component of the neurofibrillary tangles, is significantly increased in patients with AD compared with normal controls. Combining the findings for A β ₁₋₄₂ with tau appears to improve diagnostic accuracy slightly.

However, a recent paper (Engelborghs et al., 2007) found in CSF levels of A β ₁₋₄₂ and T-tau and P-tau_{181P} not to be associated with ApoE4, senile plaque or neurofibrillary tangle burden in 50 autopsy-confirmed AD patients – which is in contrast to several formerly published papers dealing with the link between CSF biomarker levels and amyloid- or tau-neuropathology. Clinically, CSF analysis requiring lumbar puncture is not as readily and repeatedly accessible as plasma. In plasma, the broad overlap in A β levels between patients with Alzheimer's disease and control individuals indicates that plasma A β cannot differentiate cases of sporadic AD from control cases. Although the significance of A β for diagnosing AD is controversial, high plasma concentrations of A β ₁₋₄₀ and low plasma concentrations of A β ₁₋₄₂ appear to indicate an increased risk of AD. Increasing evidence points to plasma A β concentration as a potential premorbid marker for the risk of AD which remains to be validated as well.

Furthermore, the known challenges of classifying Vascular Dementia (VaD) / Vascular Cognitive Impairment and differentiating between individuals who have AD versus VaD versus mixed dementia will persist because older adults are susceptible to developing cerebrovascular disease in addition to developing AD. More precise classification is required in order to study the risk factors in relation to biomarkers in older adults with dementia consistent with AD or VaD. If individuals are misclassified or misdiagnosed, then biomarker studies may result in inconsistent findings.

Beyond such problems, the translation of biomarker discoveries into clinical assays and their introduction in clinical trials is currently also facing major regulatory hurdles. All leading regulatory authorities carefully watch these developments and specifically any suggestions to use surrogate parameters as endpoints in clinical trials. While the advantages of such technologies are immediately apparent, biomarker validation remains the major concern; before such use it will be mandatory to show that a given biomarker does reliably predict the effect of the treatment on the desired clinical outcome.

In summary, there is a pressing need to modernize clinical trial methodology in AD. The developing standard of proof for a biomarker as a surrogate to reduce the length, cost and variability in AD trials is a hot topic and also closely followed at the CNS division of INC Research. INC Research is committed to provide top-notch consultancy and development solutions to the pharmaceutical industry, supporting highly specialized companies at all drug development stages in their efforts to bring new therapies to patients. By deploying our Trusted Process to manage AD and all CNS projects, continuous process improvement, consistent training, and close science follow-up are routine key elements in our daily work.

Dr. Hans Moebius is the Senior Vice President, Global Psychiatry, INC Research. With more than 17 years of strategic drug development experience in Europe, the United States and Japan, he has personally overseen the development of NCEs across a broad spectrum of CNS indications. He has worked with the FDA, EMEA and several national authorities for the successful registration of five new CNS therapies (e.g. memantine) including all aspects of pre-clinical and clinical development, regulatory strategy and establishing global pharmacovigilance strategies. Dr. Moebius is a board certified psychiatrist and neurologist.

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