Our Mission: Helping to prepare Iowa’s health practitioners to care for our growing population of elders. E-NEWS is one of our methods of teaching through technology.

Each month, E-NEWS delivers abstracts from current multidisciplinary healthcare journal articles related to a specific geriatric topic. This month’s E-NEWS focuses on NEW DIAGNOSTIC TOOLS FOR UNDERSTANDING DEMENTIA.

NEW DIAGNOSTIC TOOLS FOR UNDERSTANDING DEMENTIA

In this issue of the E-NEWS, you will find abstracts for:

- An article that discusses biomarkers for Alzheimer’s disease and other forms of dementia.
- A study that examines the use of florbetapir-PET for imaging beta-amyloid pathology.
- A study that investigates whether CSF biomarker and PIB-PET-derived beta-amyloid signature predicts changes in nondemented subjects.
- An article that reviews the study and treatment of preclinical Alzheimer’s disease.
- A study that evaluates whether integrative EEG biomarkers predict progression from mild cognitive impairment to Alzheimer's disease.
- An article that presents background information about brain amyloid imaging and its role in the diagnosis of Alzheimer's disease.
- An article that describes beta amyloid imaging in Alzheimer's disease.
- An article that reviews the accomplishments of the Alzheimer's Disease Neuroimaging Initiative.

An early diagnosis of Alzheimer's disease (AD) and other types of dementia-causing disorders is vital in order to achieve effective treatments. Fortunately, in the recent years the search for specific biomarkers has undergone a rapid evolution. New technologies in proteomics and genomics have permitted great advances in defining biochemical markers in cerebrospinal fluid (CSF) and in blood. Novel imaging techniques are also improving the diagnosis and early detection of brain changes in vivo. Furthermore, combined analysis of different biomolecules, or of biochemical and neuroimaging studies, increase diagnostic sensitivity and specificity. However, the discovery of sensitive and specific biomarkers for neurodegenerative diseases needs to overcome some important challenges. With the available technology, standardization of methods is essential to reducing inconsistency and increasing reliability. Global initiatives, multicenter studies and consensus protocols of analysis are of critical importance. The present review summarizes the results achieved in the search for an early diagnosis of neurodegenerative disorders, and reflects the limitations and the perspectives of the field. Copyright Elsevier Inc.


CONTEXT: The ability to identify and quantify brain β-amyloid could increase the accuracy of a clinical diagnosis of Alzheimer disease. OBJECTIVE: To determine if florbetapir F 18 positron emission tomographic (PET) imaging performed during life accurately predicts the presence of β-amyloid in the brain at autopsy. DESIGN, SETTING, AND PARTICIPANTS: Prospective clinical evaluation conducted February 2009 through March 2010 of florbetapir-PET imaging performed on 35 patients from hospice, long-term care, and community health care facilities near the end of their lives (6 patients to establish the protocol and 29 to validate) compared with immunohistochemistry and silver stain measures of brain β-amyloid after their death used as the reference standard. PET images were also obtained in 74 young individuals (18-50 years) presumed free of brain amyloid to better understand the frequency of a false-positive interpretation of a florbetapir-PET image. MAIN OUTCOME MEASURES: Correlation of florbetapir-PET image interpretation (based on the median of 3 nuclear medicine physicians' ratings) and semiautomated quantification of cortical retention with postmortem β-amyloid burden, neuritic amyloid plaque density, and neuropathological diagnosis of Alzheimer disease in the first 35 participants autopsied (out of 152 individuals enrolled in the PET pathological correlation study). RESULTS: Florbetapir-PET imaging was performed a mean of 99 days (range, 1-377 days) before death for the 29 individuals in the primary analysis cohort. Fifteen of the 29 individuals (51.7%) met pathological criteria for Alzheimer disease. Both visual interpretation of the florbetapir-PET images and mean quantitative estimates of cortical uptake were correlated with presence and quantity of β-amyloid pathology at autopsy as measured by immunohistochemistry (Bonferroni p, 0.78 [95% confidence interval, 0.58-0.89]; P <.001) and silver stain neuritic plaque score (Bonferroni p, 0.71 [95% confidence interval, 0.47-0.86]; P <.001). Florbetapir-PET images and postmortem results rated as positive or negative for β-amyloid agreed in 96% of the 29 individuals in the primary analysis cohort. The florbetapir-PET image was rated as amyloid negative in the 74 younger individuals in the nonautopsy cohort. CONCLUSIONS: Florbetapir-PET imaging was correlated with the presence and density of β-amyloid. These data provide evidence that a molecular imaging procedure can identify β-amyloid pathology in the brains of individuals during life. Additional studies are required to understand the appropriate use of florbetapir-PET imaging in the clinical diagnosis of Alzheimer disease and for the prediction of progression to dementia.

Beta-amyloid (Aβ) is a histopathological hallmark of Alzheimer's disease dementia, but high levels of Aβ in the brain can also be found in a substantial proportion of nondemented subjects. Here we investigated which 2-year rate of brain and cognitive changes are present in nondemented subjects with high and low Aβ levels, as assessed with cerebrospinal fluid and molecular positron emission tomography (PET)-based biomarkers of Aβ. In subjects with mild cognitive impairment, increased brain Aβ levels were associated with significantly faster cognitive decline, progression of gray matter atrophy within temporal and parietal brain regions, and a trend for a faster decline in parietal Fludeoxyglucose (FDG)-PET metabolism. Changes in gray matter and FDG-PET mediated the association between Aβ and cognitive decline. In contrast, elderly cognitively healthy controls (HC) with high Aβ levels showed only a faster medial temporal lobe and precuneus volume decline compared with HC with low Aβ. In conclusion, the current results suggest not only that both functional and volumetric brain changes are associated with high Aβ years before the onset of dementia but also that HC with substantial Aβ levels show higher Aβ pathology resistance, lack other pathologies that condition neurotoxic effects of Aβ, or accumulated Aβ for a shorter time period.


Researchers have begun to characterize the subtle biological and cognitive processes that precede the clinical onset of Alzheimer disease (AD), and to set the stage for accelerated evaluation of experimental treatments to delay the onset, reduce the risk of, or completely prevent clinical decline. In this Review, we provide an overview of the experimental strategies, and brain imaging and cerebrospinal fluid biomarker measures that are used in early detection and tracking of AD, highlighting at-risk individuals who could be suitable for preclinical monitoring. We discuss how advances in the field have contributed to reconceptualization of AD as a sequence of biological changes that occur during progression from preclinical AD, to mild cognitive impairment and finally dementia, and we review recently proposed research criteria for preclinical AD. Advances in the study of preclinical AD have driven the recognition that efficacy of at least some AD therapies may depend on initiation of treatment before clinical manifestation of disease, leading to a new era of AD prevention research.


Alzheimer's disease (AD) is a devastating disorder of increasing prevalence in modern society. Mild cognitive impairment (MCI) is considered a transitional stage between normal aging and AD; however, not all subjects with MCI progress to AD. Prediction of conversion to AD at an early stage would enable an earlier, and potentially more effective, treatment of AD. Electroencephalography (EEG) biomarkers would provide a non-invasive and relatively cheap screening tool to predict conversion to AD; however, traditional EEG biomarkers have not been considered accurate enough to be useful in clinical practice. Here, we aim to combine the information from multiple EEG biomarkers into a diagnostic classification index in order to improve the accuracy of predicting conversion from MCI to AD within a 2-year period. We followed 86 patients initially diagnosed with MCI for 2 years during which 25 patients converted to AD. We show that multiple EEG biomarkers mainly related to activity in the beta-frequency range (13-30 Hz) can predict conversion from MCI to AD. Importantly, by integrating six EEG biomarkers into a diagnostic index using logistic regression the prediction improved compared with the classification using the individual biomarkers, with a sensitivity of 88% and specificity of 82%, compared with a sensitivity of 64% and specificity of 82% of the best individual biomarker in this index. In order to identify this diagnostic index we developed a data mining approach implemented in the Neurophysiological Biomarker Toolbox (http://www.nbtwiki.net/). We suggest that this approach can be used to identify optimal combinations of biomarkers (integrative biomarkers) also in other modalities. Potentially, these integrative biomarkers could be more sensitive to disease progression and response to therapeutic intervention.

Imaging of brain β-amyloid plaques with (18)F-labeled tracers for PET will likely be available in clinical practice to assist the diagnosis of Alzheimer disease (AD). With the rapidly growing prevalence of AD as the population ages, and the increasing emphasis on early diagnosis and treatment, brain amyloid imaging is set to become a widely performed investigation. All physicians reading PET scans will need to know the complex relationship between amyloid and cognitive decline, how to best acquire and display images for detection of amyloid, and how to recognize the patterns of tracer binding in AD and other causes of dementia. This article will provide nuclear medicine physicians with the background knowledge required for understanding this emerging investigation, including its appropriate use, and prepare them for practical training in scan interpretation.


The introduction of radiotracers for the non-invasive in vivo quantification of amyloid-β (Aβ) burden in the brain has revolutionized the approach to the evaluation of Alzheimer's disease (AD). Aβ burden as measured by positron emission tomography (PET) matches histopathological reports of Aβ distribution in aging and dementia. It appears more accurate than FDG for the diagnosis of AD, and is an excellent aid in the differential diagnosis of AD from frontotemporal lobar degeneration. Apolipoprotein E 4 carriers, independent of diagnosis or disease severity, present with higher Aβ burden than non-4 carriers. As new therapies enter clinical trials, the role of Aβ imaging in vivo is becoming increasingly crucial. Aβ imaging allows the in vivo assessment of brain Aβ pathology and its changes over time, providing highly accurate, reliable, and reproducible quantitative statements of regional or global Aβ burden in the brain, essential for therapeutic trial recruitment and for the evaluation of anti-Aβ treatments. Although Aβ burden as assessed by PET does not strongly correlate with cognitive impairment in AD, it does correlate with memory impairment and a higher risk for cognitive decline in the aging population and mild cognitive impairment (MCI) subjects. This correlation with memory impairment, one of the earliest symptoms of AD, suggests that Aβ deposition is not part of normal aging, supporting the hypothesis that Aβ deposition occurs well before the onset of symptoms and likely represents preclinical AD in asymptomatic individuals and prodromal AD in MCI. Further longitudinal observations, coupled with different disease-specific biomarkers to assess potential downstream effects of Aβ, are required to confirm this hypothesis and further elucidate the role of Aβ deposition in the course of AD.


The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an ongoing, longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD). The study aimed to enroll 400 subjects with early mild cognitive impairment (MCI), 200 subjects with early AD, and 200 normal control subjects; $67 million funding was provided by both the public and private sectors, including the National Institute on Aging, 13 pharmaceutical companies, and 2 foundations that provided support through the Foundation for the National Institutes of Health. This article reviews all papers published since the inception of the initiative and summarizes the results as of February 2011. The major accomplishments of ADNI have been as follows: (1) the development of standardized methods for clinical tests, magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebrospinal fluid (CSF) biomarkers in a multicenter setting; (2) elucidation of the patterns and rates of change of imaging and CSF biomarker measurements in control subjects, MCI patients, and AD patients. CSF biomarkers are consistent with disease trajectories predicted by β-amyloid cascade (Hardy, J Alzheimers Dis 2006;9(Suppl 3):151-3) and tau-mediated neurodegeneration hypotheses for AD, whereas brain atrophy and hypometabolism levels show predicted patterns but exhibit differing rates of change depending on region and disease severity; (3) the assessment of alternative methods of diagnostic categorization. Currently, the best
classifiers combine optimum features from multiple modalities, including MRI, [(18)F]-fluorodeoxyglucose-PET, CSF biomarkers, and clinical tests; (4) the development of methods for the early detection of AD. CSF biomarkers, β-amyloid 42 and tau, as well as amyloid PET may reflect the earliest steps in AD pathology in mildly symptomatic or even nonsymptomatic subjects, and are leading candidates for the detection of AD in its preclinical stages; (5) the improvement of clinical trial efficiency through the identification of subjects most likely to undergo imminent future clinical decline and the use of more sensitive outcome measures to reduce sample sizes. Baseline cognitive and/or MRI measures generally predicted future decline better than other modalities, whereas MRI measures of change were shown to be the most efficient outcome measures; (6) the confirmation of the AD risk loci CLU, CR1, and PICALM and the identification of novel candidate risk loci; (7) worldwide impact through the establishment of ADNI-like programs in Europe, Asia, and Australia; (8) understanding the biology and pathobiology of normal aging, MCI, and AD through integration of ADNI biomarker data with clinical data from ADNI to stimulate research that will resolve controversies about competing hypotheses on the etiopathogenesis of AD, thereby advancing efforts to find disease-modifying drugs for AD; and (9) the establishment of infrastructure to allow sharing of all raw and processed data without embargo to interested scientific investigators throughout the world. The ADNI study was extended by a 2-year Grand Opportunities grant in 2009 and a renewal of ADNI (ADNI-2) in October 2010 through to 2016, with enrollment of an additional 550 participants.

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Next Month’s Issue:
Financial Exploitation in Aging and Dementia

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