Alzheimer's Disease: The Future of Diagnosis, Prevention and Treatment

Contributed by Michael Rosenbloom, M.D.

Introduction

Alzheimer's disease is the most common cause of dementia, accounting for 60 to 80 percent of cases and affecting 5.3 million individuals. It is also the sixth leading cause of death and the only one of the top 10 causes of death for which there is no treatment, prevention or cure.[1] An estimated 90,000 Minnesotans have the condition. Although the prevalence and associated costs of Alzheimer's disease are expected to triple by 2050, 27-81% of physicians may fail to recognize the disease.[2] In addition, the last time the U.S. Food and Drug Administration (FDA) approved a drug for Alzheimer's was more than 10 years ago. Fortunately, dementia research conducted in Minnesota and throughout the country is expected to make significant progress in diagnosis, prevention and treatment of Alzheimer's.

Diagnosis

A definite Alzheimer's diagnosis requires pathological confirmation of cerebral amyloid plaques and neurofibrillary tangles from brain tissue. Despite the reliance on diagnostic measures such as cognitive screening tests, neuropsychological testing, laboratory studies and neuroimaging, clinicians can, at most, provide a diagnosis of "probable Alzheimer's." Thus, Alzheimer's is distinct from other chronic conditions such as diabetes or cancer in that the pre-mortem diagnosis is never guaranteed; standard diagnostic tests' sensitivity and specificity for Alzheimer's are 70.9 to 87.3% and 44.3 to 70%, respectively.[3]

Following the release of the revised 2011 National Institute on Aging-Alzheimer's Association criteria for Alzheimer's,[4] this condition is now viewed as existing on a continuum of three separate stages: preclinical, mild cognitive impairment and dementia. Whereas mild cognitive impairment and dementia were already well-defined, the preclinical stage — a state in which patients lack cognitive symptoms but have evidence of Alzheimer's-related brain changes — emerged as a research focus. In support of this concept, investigations of asymptomatic carriers of autosomal-dominant Alzheimer's disease have shown disease-related changes such as altered cerebral amyloidosis and increased spinal fluid tau 15 to 25 years before the expected disease onset.[5]

The concept of preclinical Alzheimer's disease has inspired an explosion of research pertaining to serum, cerebrospinal fluid and imaging biomarkers intended to facilitate identification of Alzheimer's disease. Alterations in cerebrospinal fluid levels of Abeta42 (decreased), tau (increased) and phospho-tau (increased) have been documented in early-stage Alzheimer's.[6] In addition, cerebrospinal fluid studies are occasionally used clinically to support a diagnosis. Amyloid positron emission tomography (PET), which consists of administration of a radioactive ligand that specifically binds to brain amyloid, has enabled clinicians and researchers to detect amyloid plaques in vivo. The earliest amyloid PET scans used Pittsburg Compound B, a carbon (C)11 radioisotope with a 20-minute half-life, which limited scanning to institutions with cyclotrons. However, fluorine(F)18 tracers, which have half-lives of 110 minutes, have enabled this diagnostic technique to be used in clinics throughout the country.

Although three F18 compounds are FDA-approved (flobetapir, flutametamol and florbetaben), the Centers for Medicare & Medicaid Services ruled in 2013 that the evidence was insufficient to conclude that amyloid PET imaging was necessary for diagnosis or treatment of Alzheimer's. The Imaging Dementia Evidence for Amyloid Scanning trial (IDEAS), led by the Alzheimer's Association and the American College of Radiology Imaging Network, is a study designed to assess the practical clinical application of amyloid PET imaging in atypical mild cognitive impairment and dementia. This investigation is measuring the impact of this imaging modality on medical decision-making and health care usage. A total of 18,488 Medicare beneficiaries aged 65 and older will be enrolled over 24 months at roughly 200 sites throughout the United States. If evidence suggests that this diagnostic procedure significantly affects clinical care, amyloid PET imaging could be reimbursable for atypical presentations of mild cognitive impairment and dementia. The HealthPartners Center for Memory and Aging in Saint Paul, MN is a physician referral and imaging site for the IDEAS study.

Confirmation of cerebral amyloid is necessary but not sufficient for a diagnosis of definite Alzheimer's disease. Whereas amyloid imaging was an important step

in documenting the pathological signature of Alzheimer's disease, this test is limited in that it fails to provide any information related to the deposition of neurofibrillary tangles and neurodegeneration — both common pathological changes in Alzheimer's. Tau-PET imaging is the most recent imaging biomarker to detect brain pathological changes; the technique not only enables assessment of aggregated tau but also allows visualization of the neuroanatomical distribution. Specifically, Mayo Clinic in Rochester, MN has been using the PET tracer 18F-AV-1451 in both preclinical and Alzheimer's disease, finding that imaging results effectively track disease progression.

Between the IDEAS study and ongoing investigations into tau-PET imaging, the future of the diagnosis of Alzheimer's may be simplified. However, whether PET imaging with radioactive ligands will revolutionize the diagnosis and treatment of Alzheimer's disease remains to be seen.

In addition to PET imaging, cognitive screening may be another way to facilitate early diagnosis of Alzheimer's. Minnesota-based health care organizations, including Allina, Essentia, and HealthPartners, have explored or are exploring the role of cognitive screening in asymptomatic elderly subjects and its effects on health care outcomes.

Prevention

One of the most common questions is whether Alzheimer's disease is preventable. Longitudinal cohort studies have shown that the risk of late-life dementia is decreased in individuals with routine physical activity, social activity and cognitive stimulation. In addition, effective measures to reduce physical inactivity, depression, smoking, midlife hypertension, midlife obesity and diabetes may reduce the incidence of Alzheimer's by up to one third.[7]

The design of clinical trials on the prevention of Alzheimer's disease is particularly challenging due to the lack of a definitive predictive biomarker and the indolent disease progression. Consequently, a variety of multisite clinical trials are following and treating populations at highest risk for AD. The Alzheimer's Prevention Initiative, a collaboration of the Banner Institute, the pharmaceutical industry and the National Institute of Health, is a longitudinal study of an extended family in Colombia carrying the presenilin 1 mutation in which offspring have a 50% chance of developing autosomal-dominant Alzheimer's. In this condition, cognitive decline typically manifests by age 45. The Autosomal Dominant Alzheimer's Disease Trial is testing the effects of the anti-amyloid antibody crenezumab in delaying cognitive symptoms in this population. Likewise, the Dominantly Inherited Alzheimer's Network through Washington University is investigating longitudinal biomarkers in disease carriers.

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's study, funded by the National Institute on Aging, Eli Lilly and Company and several philanthropic organizations, is aimed at preventing Alzheimer's. The study will enroll 1,000 adults aged 65 to 85 with positive amyloid PET studies (i.e., biomarker evidence for Alzheimer's) but no evidence of cognitive impairment. Eventually, subjects will receive an investigational amyloid antibody treatment. Outcomes related to cognition and development of Alzheimer's will be compared between the investigational drug and placebo group. Mayo Clinic is a research site for this trial.

Treatment

The limited number of cognitive-enhancing and disease-modifying Alzheimer's therapies has promoted extensive investigation into potential therapeutic agents. Since cerebral amyloidosis was identified as one of the earliest Alzheimer's disease-related changes, numerous ongoing clinical trials have been conducted to inhibit the amyloid pathway in early-stage disease. Previously, clinical trials recruited patients with mild to moderate Alzheimer's disease. However, the current trend is to identify subjects at the earliest stage detectable in the clinical setting, namely mild cognitive impairment or prodromal Alzheimer's disease. Merck is studying the effects of a beta-secretase 1 inhibitor intended to block the production of amyloid on the progression of mild cognitive impairment to Alzheimer's disease in prodromal Alzheimer's. In addition, Genentech is conducting a phase 3 clinical trial of crenezumab, which binds specifically to Abeta peptides in subjects with mild cognitive impairment or Alzheimer's.

In addition to cerebral amyloidosis, the Alzheimer's disease brain shows impairments in central nervous system insulin signaling and metabolism. Findings indicating impaired insulin production and signaling have linked Alzheimer's disease and diabetes mellitus. Consequently, Alzheimer's disease has been called a "type 3 diabetes mellitus of the brain".[8] These insulin deficits have provided the scientific foundation for two ongoing clinical trials in Alzheimer's disease. The National Institute on Aging-funded Study of Nasal Insulin to Fight Forgetfulness is testing intranasal insulin in mild cognitive impairment and Alzheimer's at sites throughout the country, including Mayo Clinic. The HealthPartners Center for Memory and Aging is conducting a phase II, double-blinded, placebo-controlled trial of the rapid-acting insulin IN glulisine to measure its effects on cognition and disease progression in mild cognitive impairment and Alzheimer's.

Finally, Fang Yu, Ph.D., at the University of Minnesota is evaluating the effect of routine aerobic exercise on cognition in Alzheimer's disease through the FIT-AD trial. Outcomes related to exercise also will be compared with traditional pharmacotherapy in this patient population.

Conclusion

Due to challenges associated with diagnosis, prevention and treatment, Alzheimer's disease remains one of the most formidable chronic conditions. Ongoing research into the relationships among early-stage Alzheimer's disease, amyloidosis and tau deposition will be critical in shaping the diagnostic approach and clinical trials of the future. In addition, novel treatments aimed at addressing the underlying mechanism of disease, whether it is related to amyloid deposition, tau aggregation or central nervous system metabolic disarray, provide optimism for an eventual treatment or cure for this devastating neurodegenerative disease. ✦

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References available upon request.

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