Alzheimer's disease: New horizons on diagnosis and treatment

Robert Goldman

Chairman, American Academy of Anti-Aging Medicine (A4M)
Professor, Department of Internal Medicine at the Central America Health Sciences University of Medicine (Belize)
Professor, Postgraduate Studies at Graduate School of Medicine at Swineburne University (Australia)

Abstract

There exists a clear urgency to the search to prevent and cure Alzheimer's disease. Scientists from Rush-Presbyterian-St Luke's Medical Center (Chicago, IL USA) and the US Centers for Disease Control and Prevention (CDC) predict that the numbers of Americans afflicted will increase dramatically, from 4.5 million in 2000 to 5.1 million in 2010, 5.7 million in 2020, 7.7 million in 2030, 11 million in 2040, and reach 13.2 million in 2050. This skyrocketing trend is expected to become one of the nation's, and world's, greatest public health challenges in the coming decades. Since the 1970s, increasing international efforts have focused on the diagnosis, prevention, and treatment of Alzheimer's Disease. A cure has remained elusive. In this article, we review the latest scientific literature published in 2004 concerning the diagnosis and treatment of Alzheimer's Disease.

Key words: Alzheimer's Disease (AD); cognitive function; amyloid plaques; neurofibrillary tangles; AD risk factors; AD diagnosis; AD prevention; AD treatment

Introduction

Alzheimer's disease (AD) is a degenerative brain syndrome characterized by a progressive decline in cognitive functions such as memory, thinking, comprehension, calculation, language, learning capacity and judgement. AD is a slow disease, with the course and progression varying from person to person. The time from diagnosis to death varies, from as little as 3 to 4 years if the patient is 80 or over when diagnosed, to 10 or 20 years if the patient is younger at diagnosis. For all AD patients, their condition deteriorates over time.

Worldwide Statistics

The World Health Organization (WHO) estimates that worldwide, 37 million people worldwide live with dementia, with Alzheimer's disease causing the majority of cases. The onset of AD is usually after 65 years of age, though earlier onset is not uncommon. As age advances, the incidence increases rapidly: for every 5-year age group beyond 65, the percentage of people with AD doubles. Among people age 60 and over, about 5% of men and 6% of women around the worlds are affected. There is no evidence of any sex difference in incidence, but more women encounter AD because of greater female longevity.

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Reprint requests to: Dr. Robert Goldman. American Academy of Anti-Aging Medicine 1510 West Montana Street Chicago, IL 60614 USA. Tel: (773) 528-4333 Fax: (773) 528-5390
Email: bgoldman@worldhealth.net
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With the global aging of populations, most pronounced in the world's industrialized regions, the incidence of AD is projected to show a rapid increase in the next 20 years.

US Statistics

In the United States, an estimated 4 million people now have AD. Of these, about 3% of men and women ages 65 to 74 have AD, and nearly half of those age 85 and older may have the disease.

Researchers have estimated that the number of new cases every year will double between 1995 and 2050, increasing from 377,000 to stand at 959,000 (see Figure 1). Two factors are responsible for this large increase:

- The fact that the risk of AD increases as people get older.
- The growing numbers of older people, especially those over 85, the population bracket at the greatest risk for AD.

Consequently, by 2050, 14 million older Americans are expected to have Alzheimer's disease, if the current numbers hold and no preventive treatments become available.

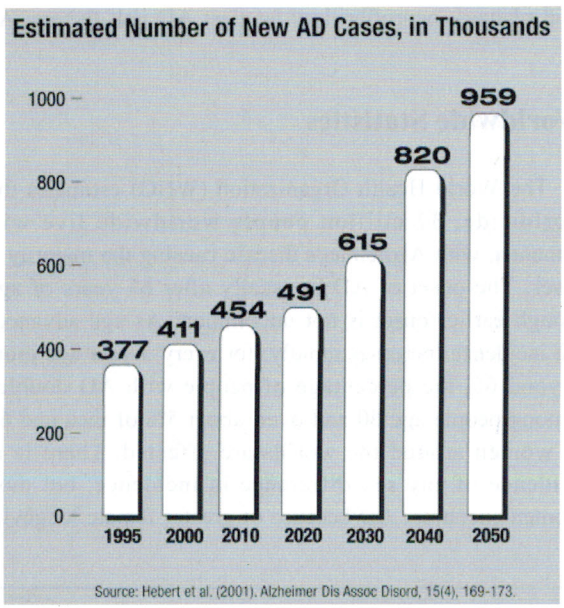

Figure 1. The Projected Steep Climb in Diagnosed AD Cases (United States)

The Staggering Costs of AD

The cost of AD to society is already massive and will continue to increase. In the United States, the national cost of caring for people with AD is now estimated at $100 billion every year. The cost of care is not only financial. Families, friends, and caregivers struggle with great emotional and physical stress as they cope with the physical and mental changes in their loved ones. Caregivers must juggle many responsibilities and adjust to new and changing roles. As the disease gets worse and caring at home becomes increasingly difficult, family members face difficult decisions about long-term care. The number of caregivers, and their needs, will steadily grow as our population ages and the number of people with AD increases.

History & New Knowledge

Alzheimer's Disease is named after Dr. Alois Alzheimer, a German doctor. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. He found abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary tangles). Today, these plaques and tangles in the brain are considered hallmarks of AD.

Twenty-five years ago, other than some basics, scientists knew very little about AD. Today, thanks to advancements in medical technology, an early diagnosis of AD is possible, a handful of medications have been developed to mitigate symptoms, and, while there presently is no cure for the disease, there are a host of promising treatments in the pipeline. Research conducted over the last two decades has deepened our understanding of this devastating disease. It also has expanded our knowledge of brain function in healthy older people and identified ways that science might be able to lessen normal age-related declines in mental function.

There exists a clear urgency to the search to prevent and cure Alzheimer's disease. Scientists from Rush-Presbyterian-St Luke's Medical Center (Chicago, IL USA) and the US Centers for Disease Control and Prevention (CDC) predict that the numbers of Americans afflicted will increase dramatically, from 4.5 million in 2000 to 5.1 million in 2010, 5.7 million in 2020, 7.7 million in 2030, 11 million in 2040, and reach 13.2 million in 2050. This skyrocketing trend is expected to become one of the nation's, and world's, greatest public health challenges in the coming decades.

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Discoveries in AD Information & Diagnosis

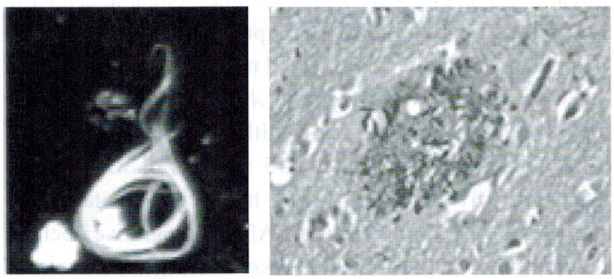

Figure 2. Neurofibrillary tangles of tau protein (left) and beta amyloid plaques (right) in the brain characterize AD

Familial AD and Herpes Simplex Virus Type 1. Dr. Isamu Mori and colleagues from Aichi Medical University School of Medicine (Aichi, Japan) used nested PCR to study brain tissue from individuals with familial AD and individuals with sporadic AD. Herpes Simplex Virus Type 1 (HSV-1) was detected in all cases. In a related study of the brains of the individuals with familial AD, high-sensitivity immunohistochemistry revealed HSV-1 antigens in the cytoplasm of cortical neurons, providing the first evidence of reactivation of HSV-1 associated with beta-amyloid deposition. The possible involvement of HSV-1 in conjunction with genetic factors suggests that infection may contribute to the etiology of familial AD.

Diabetics at increased risk of developing AD. In a longitudinal cohort study involving 824 Catholic nuns, priests, and brothers age 55 and over, Dr. Zoe Arvanitakis and colleagues from the Rush Alzheimer's Disease Center, the Department of Neurological Sciences, Rush University Medical Center (Chicago, IL, USA) determined that diabetes mellitus was present in 127 (15.4%) of the participants. During a mean of 5.5 years of observation, 151 persons developed AD. In a proportional hazards model adjusted for age, sex, and educational level, those with diabetes mellitus had a 65% increase in the risk of developing AD compared with those without diabetes mellitus (hazard ratio, 1.65; 95% confidence interval, 1.10-2.47). In random effects models, diabetes mellitus was associated with lower levels of global cognition, episodic memory, semantic memory, working memory, and visuospatial ability at baseline. Diabetes mellitus was associated with a 44% greater rate of decline in perceptual speed (P =.02), but not in other cognitive systems. The researchers conclude that: "Diabetes mellitus may be associated with an increased risk of developing AD and may affect cognitive systems differentially."

Low TSH as risk factor for AD. Dr. van Osch and colleagues from the University of Oxford and Radcliffe Infirmary (United Kingdom) found that AD patients had significantly lower levels of thyroid stimulating hormone (TSH) than control subjects. Lower TSH was associated with a 2.36-time increased risk of AD (95% CI=1.19 to 4.67), independent of other risk factors and confounding variables.

Antibody marker for AD found. In a study appearing in the journal Neurobiology of Aging, Dr. Mruthinti and colleagues from the Alzheimer's Research Center, Department of Pharmacology and Toxicology, Medical College of Georgia (Augusta, GA USA) found that leukocytes in AD patients contain four-times the levels of markers for amyloid-b peptide and receptor for advanced glycation end products (RAGE) than in non-AD subjects. The research could lead to a way to identify people at-risk for AD and enable the establishment of an early diagnosis.

Androgen loss may lead to AD. Dr. Christian Pike and team from the University of Southern California (USA) reported in JAMA's September 22, 2004 issue that "age-related testosterone depletion is one of the important changes that promote Alzheimer's disease in men." Further, Dr. Pike stated that "testosterone has at least two critical brain functions relevant to AD. It protects neurons from injury, and it reduces levels of beta-amyloid. The loss of testosterone with advancing age creates a more hostile neural environment." He and his colleagues also suggest that the brain is like any other tissue that experiences the effects of testosterone loss with age, and that increased vulnerability to AD should be considered a component of the clinical syndrome known as androgen deficiency in aging males (ADAM).

Low hemoglobin levels as risk factor for AD. Dr. Pandav and colleagues from the University of Pittsburgh Medical School (Pennsylvania, USA) evaluated hemoglobin levels in persons age 55 and over living in India, one of the countries that is aging rapidly and in which anemia is a common medical problem. Low hemoglobin was found to correlate to AD, and the researchers suggest further research to establish hemoglobin as a modifiable risk factor for the disease.

Discoveries in AD Prevention

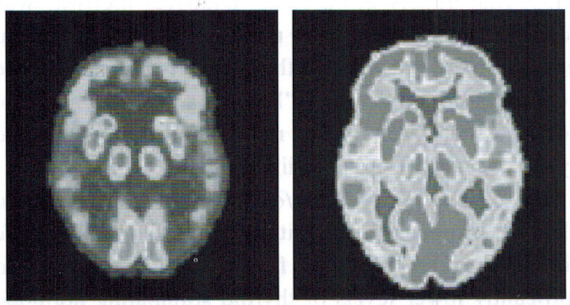

Figure 3. Compared to a normal brain (left), a brain in advanced AD (right) displays severely enlarged ventricles, as well as extreme shrinkage of the hippocampus and cerebral cortex

Combination of vitamins E and C reduce AD risk. In a cross-sectional, prospective study involving 104 cases of AD, Dr. Zandi and colleagues from the Bloomberg School of Public Health, The Johns Hopkins University (Baltimore, MD USA) administered various combinations of vitamin E (400 to 800 IU), vitamin C (500 to 1,000 mg), and a multivitamin. The team found that vitamin E and C intake was associated with a 22% reduction in AD incidence at baseline, and a 36% reduction in AD prevalence at follow-up. When taken alone, neither the multivitamins nor vitamins E or C produced a protective effect on AD risk. However, taking vitamin E with a multivitamin containing vitamin C trended toward a lower AD risk. The researchers presume that when water-soluble vitamin C is oxidized, it activates the fat-soluble vitamin E, making vitamin E better able to scour free radicals and be oxidized itself.

Low vitamin B12 is associated with poorer memory in older people with familial AD. A large-scale study by Dr. David Bunce from Goldsmith's College, University of London (United Kingdom) and colleagues from Stockholm, Sweden revealed that among healthy people over the age of 75 who have the APOe-4 gene and are thus at higher risk for AD, low levels of vitamin B12 are associated with significantly worse performance on memory tests. Conversely, carriers of the APOe-4 allele with normal B12 levels scored higher on verbal memory tests. The researchers suggest that: "APOe-4 carriers may derive relatively greater cognitive benefits from B12 and folate supplements."

Brown rice may counteract onset of AD. Publishing their findings in the Biological & Pharmaceutical Bulletin (Pharmaceutical Society of Japan), a Japanese research team found that pre-germinated brown rice (rice that has been soaked in water to induce slight germination) significantly improved the spatial learning ability in mice. Pre-germinated brown rice contains 13 times the amount of oryzanol and 15 times the gamma-amino butyric acid (GABA) of polished rice. Oryzanol contains ferulic acid ester, a free radical scavenger that the researchers suspect may offset oxidative stress that may contribute to beta amyloid damage. GABA may enhance glutamate release and the sensitivity of NMDA receptors, activation of which is thought to underlie learning and memory.

Niacin may protect against AD. Dr. Martha Morris from the Rush Institute for Healthy Aging (Chicago, IL USA) and colleagues studied 815 subjects of whom, after four years, 131 developed AD. A high level of total niacin intake seemed to protect against AD and cognitive decline. Compared with the lowest intake, the highest levels of niacin intake "was linked to an 80% reduction in risk," remarked Dr. Morris. The findings may prompt changes to current dietary guidelines for the elderly.

Discoveries in AD Treatment

RNA interference silences alleles responsible for AD. Dr. Miller and colleagues from the University of Iowa (Iowa City, IA USA) designed a method to produce small interfering RNA (siRNA) to counteract the tau mutation (V337M) and AAP mutation (APPsw) responsible for the proteins that characterize AD. The allele-specific RNA duplexes produced by this method then served as templates with which the researchers constructed short hairpin RNA (shRNA) plasmids that successfully silenced mutant tau and APP alleles.

Gene therapy surgery helps AD. Dr. Mark Tuszynski and team from the University of California/San Diego (USA) increased the brain activity of eight men and women with early-stage AD by implanting genetically engineered cells. Dr. Tuszynski's team took skin samples from each subject, and genetically modified them to make the cells produce extra nerve growth factor, a protein that prevents cell death and stimulates cell function. The respective cells were then implanted into each patient from whom they originated. In all eight participants, the gene therapy surgery resulted with increased brain activity that seemed to slow the progression of AD over time. Dr. Tuszynski is hopeful that long-term follow-up will determine the viability of proceeding to larger, controlled trials of gene therapy surgery as a treatment for AD.

Two new AD drugs in final stages of trials. Two experimental AD drugs have the potential to prevent or halt the progress of AD. Alzhemed, made by Montreal, Canada-based Neurochem Inc., is a pill currently in Phase III trials. In a study at Georgetown University Medical Center (Washington, DC USA), 58 subjects with AD took Alzhemed for a total of 24 months, at which time a significant drop in the level of beta-amyloid was found. Among patients who b+ & Co.'s LY450139 seeks to prevent beta-amyloid accumulation. A trial of 37 healthy adults over age 45 found blood levels of beta-amyloid were reduced after they took the experimental drug, which is designed to interfere with the secretases that generate beta-amyloid. The degree of reduction in beta-amyloid accumulation was dose-dependent on the amount of LY450139 administered.

Concluding Remarks

While Alzheimer's Disease was first discovered in 1906, little was known about the disorder until the latter-half of the 20th century, and a wealth of knowledge has amassed in the past decade alone. Today, it is possible to diagnose AD in its very earliest, preclinical stages. We now have a handful of medications that mitigate symptoms, and there are a host of promising new treatments in the pipeline. While there presently is no cure for the disease, medical and scientific knowledge are advancing so rapidly that, in a few years from now, there is a good chance that AD may be a thing of the past. Given that, in the absence of disease, the human brain often can function well into the tenth decade of life, a world free of Alzheimer's will rid society of the extraordinary economic burden of the disease, which currently costs $100 billion annually in the United States alone. Perhaps more importantly, the devastating emotional and physical stress the disease imposes on families, friends, and caregivers as they cope with the physical and mental changes in their loved ones will at last be lifted.

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