Alzheimer Disease and Its Growing Epidemic

Risk Factors, Biomarkers, and the Urgent Need for Therapeutics

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KEYWORDS

• Alzheimer disease • Risk factors • Biomarkers • Epidemiology

KEY POINTS

- Alzheimer disease (AD) is increasing in prevalence worldwide.
- Many individuals have preclinical AD without symptoms.
- Biomarkers are currently in development for detecting preclinical AD that may be amenable to novel therapies.
- Addressing modifiable risk factors should also help to reduce the prevalence of AD in the future.

INTRODUCTION

Alzheimer disease (AD) represents one of the greatest medical challenges of this century; the condition is becoming increasingly prevalent worldwide and as yet, no effective treatments have been developed for this terminal disease. In the United States in 2016, more than 5 million people suffer with AD, costing an approximate $236 billion. Because the disease manifests at a late stage after a long period of clinically silent

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neurodegeneration, knowledge of the modifiable risk factors and the implementation of biomarkers is crucial in the primary prevention of the disease and presymptomatic detection of AD, respectively. This article discusses the growing epidemic of AD and antecedent risk factors in the disease process. Disease biomarkers are discussed and the implications that this may have for the treatment of this currently incurable disease.

EPIDEMIOLOGY

AD is the most common dementia in the elderly and is a growing epidemic across the globe. Although the risks associated with developing AD are multifactorial, the greatest risk factor by far is aging.[1] The age-specific risk of AD dramatically increases as individuals get older; findings from the Framingham study in the early 1990s showed that the incidence doubles every 5 years up to the age of 89 years.[2] Age-dependent increases have been seen in other studies.[3–5] Unsurprisingly, with global reductions in fertility and extended life expectancies, the number of patients with AD is expected to increase as populations age.[6] In the United States, it is estimated that approximately 5.3 million people had AD in 2015; a total of 5.1 million people being 65 years and older and approximately 200,000 people younger than age 65 years with early onset AD (EOAD).[7–9] It is estimated that the number of new cases of AD and other dementias will at least double by 2050 and substantially increase the socioeconomic burden worldwide.[7,10]

In 2010, it was estimated that dementia afflicted 35.6 million people worldwide, many of which will have AD, with the projection that this figure will double every 20 years.[11] The incidence of AD is generally lower in many less economically developed countries than in North America and Europe; however, sharp rises in prevalence have been predicted and seen in China, India, and Latin America.[12,13]

The effect of this increasing dementia has obvious socioeconomic consequences for each country affected, through costs of hospital care and also of caregivers. In the United States, the total payments were estimated at $226 billion of which Medicare and Medicaid provided 68%,[7,14] whereas out-of-pocket expenses for patients and their families were expected to be $44 billion.[7]

CLASSIFICATION AND STAGING

Revised criteria and guidelines by the National Institute on Aging and the Alzheimer Association published in 2011 have recognized three stages of AD: (1) preclinical AD, (2) mild cognitive impairment (MCI) caused by AD, and (3) dementia caused by AD.[8,15] These are described as follows[7]:

1. Preclinical AD: presymptomatic of AD with early AD-related brain changes as detected by neuroimaging or other biomarker studies
2. MCI caused by AD: mild cognitive decline but still able to perform activities of daily living
3. Dementia caused by AD: cognitive decline is more pronounced and interferes with activities of daily living

With this classification in mind, it follows that the actual number of individuals with active disease is a gross underestimate because it is based on approximations of diagnosed symptomatic patients and largely ignores the vast number of individuals who are preclinical, in whom the disease process is active but asymptomatic.[16] This long preclinical phase of AD is characterized by progressive neuronal loss, the formation of neurofibrillary tangles, and the deposition of amyloid plaques within the brain.[17–20] Although the exact pathogenesis of AD is debated, the prevailing