

## Effects of Aging on Neurodegenerative Diseases

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### About the Study

Dementia is defined as a clinical syndrome characterized by progressive deterioration in multiple cognitive domains that are severe enough to interfere with daily functioning including social and professional functioning. Alzheimer's disease is the most common form of dementia often diagnosed in people over 65 years of age. Alzheimer's disease is a multifactorial disorder in the causes and the progression is still not well-understood. Alzheimer's disease is the most common neurodegenerative disorder, affecting nearly six million people in the United States and over 35 million worldwide. The illness manifests itself primarily as a decline in memory and cognition, a consequence of degeneration of the hippocampus and the neo-cortex and generally strikes those over age 65, although some 1%-2% of cases are early-onset genetic forms of the disease. On average, the course of the disease is roughly 8 years from the onset of symptoms until death, although this can be as long as 20 years. The debilitating nature of the disease, combined with the slow decline and large numbers of people affected make Alzheimer's disease highly costly to society.

Aging is the most common non-modifiable cause of dementia in the elderly, but it accounts only for approximately half of all cause. Research identified other potential causes among the interaction between modifiable environmental factors, such as vascular disease and genetic susceptibility. The recent genetic discoveries have shown that mutation of the beta-amyloid precursor protein on chromosome 21, and the mutations of presenilin 1 and presenilin 2 on chromosome 14 and 1, were associated with increased susceptibility of Alzheimer's disease. Finally, the presence of the epsilon4 allele of Apo lipoprotein is considered as a risk factor of late-onset of Alzheimer's disease. The Diagnostic and Statistical Manual on Mental Disorders, defines dementia as an acquired disease characterized by decline in memory and at least one other cognitive function such as attention, visuo-spatial skills, language or executive functions. Beside the cognition, the disease affects the emotional abilities and interferes significantly with work and daily-life activities. Dementia can be defined as either possible or probable based prospective studies of aging or its main subtypes of Alzheimer's disease and vascular dementia.

Alzheimer's disease is an age-related phenomenon and is the most common cause of dementia, but increasing evidence from population-based neuro-pathological and neuroimaging studies shows that mixed brain pathology account for a large number of dementia cases, especially in very old people. According to the World Alzheimer Report, there were 35.6 million people living with dementia worldwide in 2010, a number that will increase to 65.7 million by 2030 and 115.4 million by 2050 unless effective means of reducing disease incidence is introduced. The total estimated worldwide costs of dementia were US\$604 billion in 2010, including the costs of

informal care, direct costs of social care and the direct costs of medical care. Increasing age is a well-established risk factor for dementia and Alzheimer's disease. Both prevalence and incidence of Alzheimer's disease increases exponentially with advancing age and 70% of all dementia cases occur in people aged 75 years. Notwithstanding, despite the incidence rate of Alzheimer's disease increases almost exponentially until 85 years of age, it remains uncertain whether the incidence continues to increase even at more advanced ages or reaches a plateau. The incidence rates of Alzheimer's disease across different regions are quite similar in the younger-old but greater variations have been seen among the older ages, but this is probably because of differences in methodology such as study designs and case ascertainment.

Neurodegenerative diseases are among the most difficult biomedical problems to solve. Despite intense efforts around the world by many laboratories, both academic and industrial, little can be done for the patient who contracts one of these debilitating and deadly disorders, which include Alzheimer's disease, Parkinson's disease, front temporal dementia, amyotrophic lateral sclerosis, Huntington's disease and prion diseases. All approved therapeutics at best work at the symptomatic level; none slow or stop the inexorable loss of neurons and neuronal connections. Although tremendous progress has been made toward understanding the molecular and cellular basis of neurodegenerative diseases, this progress has yet to be translated into efficacious medicines. The failure of so many drug candidates in the clinic suggests that our understanding of disease mechanisms is still insufficient. The need to solve the problems is dire. These diseases are invariably progressive, devastatingly debilitating and ultimately lethal. As the victim becomes more and more disabled, the strain-emotional, physical and financial -on patients and their families and caregivers can become overwhelming. The healthcare costs become exorbitant and as age is generally the greatest risk factor for acquiring a neurodegenerative disorder, demographic changes suggest societies will be overburdened in the decades to come.

Perhaps the most common risk factor for neurodegeneration is age. Damage to neurons can accrue with age and the large majority of neurons are not replaced *via* neurogenesis. As neurogenesis age, they accumulate more mutations, in both nuclear and mitochondrial DNA, as reactive oxygen species increase and DNA repair mechanisms fail to compensate. Such mutations result in altered gene expression, including of genes important for learning, memory and neuronal survival. A decline in protein quality control machinery and waste disposal through the proteasome and autophagy also occurs with age and leads to buildup of toxic proteins and protein aggregates. Mitochondrial function and energy metabolism likewise lessen with age and interfere with neuronal health and function.