Alzheimer's Disease:
Epidemiology, Risks, and Testing

Hilary Henly
Head of Underwriting, Ireland
Director, Divisional Underwriting Research

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Introduction

Today, we are only just beginning to understand what causes Alzheimer's disease (AD). There is increasing concern about the lack of effective treatments that could slow down the rate of disease progression or provide a cure. The pace of progress in developing breakthrough discoveries is slow and the number of people diagnosed with Alzheimer's disease continues to grow. Dementia is a major cause of significant impairment, and in this article, we take a look at current prevalence rates, risks and the tests that are in development today.

Epidemiology

Alzheimer's disease is the most common type of dementia diagnosed today, accounting for 60-70% of the estimated 50 million people globally who suffer with dementia.[1] It is a degenerative brain disease which is understood to begin 20 years or more before symptoms become apparent in those affected. Neurons in the brain become damaged or destroyed due to the accumulation of the protein fragment beta-amyloid (Aβ) outside the neurons, called beta-amyloid plaques, as well as accumulations of an abnormal form of the protein tau inside the neurons. As a result of this build-up, the body activates immune system cells called microglia that try to clear the toxic proteins, resulting in chronic inflammation when the microglia can no longer keep up with the amount of toxins produced.

The highest prevalence and incidence rates of AD are reported in North America and Western Europe, followed by Latin America, China, and the Western Pacific. It is officially the sixth leading cause of death in the U.S., where 5.8 million Americans have been diagnosed with the disease. This figure is projected to rise to 14 million by 2050. Approximately 200,000 of those living with AD are younger than 65 years of age, but the vast majority (81%) are over age 75.[2, 3]

Risk factors

There are three stages of Alzheimer's disease: preclinical Alzheimer's disease, mild cognitive impairment and lastly dementia. Symptoms include memory loss and problems with cognition and communication. The greatest risk factors for late-onset Alzheimer's disease are older age, as well as a positive family history of the disease. Older age alone is not a cause of developing the disease and is not a normal part of ageing, but the risk of developing AD increases with age. Environmental and lifestyle factors as well as medical history are all understood to play a part in disease development, with adverse factors including having low physical activity, unhealthy eating, diabetes, smoking, obesity and dyslipidemia.[4]

In the preclinical stage of Alzheimer's disease, people have measurable changes of Aβ in the brain and cerebrospinal fluid, which are indicators of early signs of Alzheimer's disease. It is these biomarkers, as well as cognitive function tests and brain imaging, which are currently used to help diagnose the disease. Positron emission tomography (PET) scans can help in

differentiating AD from other causes of dementia such as frontotemporal dementia and Lewy body dementia. Cerebrovascular disease, which often co-exists with AD, further increases the risk of dementia. Brain infarcts may increase the deposition of aβ, leading to cognitive impairment. Individuals who have suffered a traumatic brain injury (TBI) in the past have also been found to have a higher risk of dementia.[3]

Early-onset Alzheimer's disease can develop in people aged between 30 and 60, but it accounts for less than 10% of all cases. It is estimated that 1% or less of AD cases are caused by a rare mutation of one of three specific genes. These include the gene for the amyloid precursor protein (APP) and the genes for the presenilin 1 (PSEN1) and presenilin 2 (PSEN2) proteins. People who inherit an APP mutation on chromosome 21 or a PSEN1 mutation on chromosome 14 will develop Alzheimer's disease, while those who inherit a PSEN2 mutated gene on chromosome 1 have a 95% chance of developing the disease. Symptoms are sometimes found in people as young as 30 years of age.[2]

New evidence suggests that air pollution may be responsible for an increased risk of developing Alzheimer's disease. Fine particles, referred to as PM2.5 particles, can remain airborne for long periods of time. They are easily inhaled and can deposit in large accumulations inside the body, including the brain. Researchers have found that accumulations of PM2.5 are associated with greater declines in immediate recall and new learning.[5]

Other studies have shown that people who lead an intellectually enriched life have a reduced risk of Alzheimer's disease and even in those who have developed the disease, continuing to engage in mental activities such as reading or playing games or musical instruments can help reduce the rate of memory decline. A 2005 meta-analysis of 22 studies found a 46% decreased risk of dementia in those who had a high brain reserve compared to those with a low brain reserve. Having an extensive social network has also been found to be a protective factor.[4]

Testing for Alzheimer's disease

In addition to environmental and lifestyle risk factors, there is a risk of developing Alzheimer's disease in individuals who have a specific form of the ApoE gene on chromosome 19. The e2, e3 and e4 forms of the gene ApoE influence the AD risk. Everyone inherits one of three forms of the ApoE gene: e2, e3 or e4 from each parent. This results in one of the following combinations: e2/e2, e2/e3, e2/e4, e3/e3, e3/e4 or e4/e4 alleles. Having an e4 ApoE allele increases the risk of developing Alzheimer's disease, while having an e2 ApoE allele is understood to reduce a person's risk of Alzheimer's disease. Those with the e4 form are more likely to develop symptoms of Alzheimer's at a younger age, and those who inherit two copies of the e4 allele have an eight- to twelvefold risk. Furthermore, each inherited ApoE e4 allele lowers the age-at-onset by six to seven years. [2,3]

While specific blood tests can show which forms of the ApoE allele a person has, it still cannot predict who will or will not develop Alzheimer's disease.[6]

The ApoE gene is responsible for giving instructions to make ApoE protein, which then combines with lipids to form molecules called lipoproteins. ApoE can reflect AD status when measured in blood serum and plasma. Wang et al.'s meta-analysis found that in the eight studies included, a lower level of peripheral blood ApoE was recorded in Alzheimer's disease patients.[6]

Present methods of testing for AD are aimed at identifying people who may have an increased risk of developing the disease. In 2017, the U.S. Food and Drug Administration (FDA) approved an at-home saliva test that looks for specific genetic markers associated with late-onset Alzheimer's disease. The test evaluates whether a person has the ApoE e4 allele only and does not test for e2 or e3. The test does not rule in or rule out a diagnosis of Alzheimer's disease, nor does it confirm to what extent a person is at increased risk of Alzheimer's. More than half of patients with late-onset disease do not carry the e4 allele, and the population-attributable risk related to carrying an e4 allele is estimated at only 20%.[4]

To date, genome-wide association studies (GWAS) have identified 19 other significant markers of AD, aside from ApoE e4. These markers have been combined into a polygenic risk score (PRS), along with 80,000 less strongly associated genetic markers, which has achieved an ability to predict the onset of AD in 78% of cases.[7]

A new test currently in development uses mass spectrometry to measure amyloid beta 42 (Aβ42) and amyloid beta 40 (Aβ40) in the blood. Its aim is to identify early brain changes in AD and to predict whether Aβ has accumulated in the brain. When the results were combined with two other risk factors (age and the presence of e4), 94% of people from the study were accurately identified as having early AD brain changes. It is hoped that the blood test will allow for thousands of people to be screened each month, ultimately saving on the cost of screening through PET scans.[8,9]

Other tests being developed include a blood test to identify a rare form of Alzheimer's disease, known as dominantly inherited Alzheimer's disease (DIAD), or autosomal dominant AD. It arises from a mutation from one of the APP, PSEN1 or PSEN2 genes. The test is designed to look for changes in the levels of neurofilament light chain (NfL) protein, a protein which is normally found within brain neurons. Damaged and dead neurons can leak this protein into cerebrospinal fluid, which then can be further detected in blood. However, NfL protein can also leak into cerebrospinal fluid as a result of Huntington's disease, Lewy body dementia, multiple sclerosis and traumatic brain injury.[10]

There are as yet no pharmaceutical drugs available that can stop the progression of or cure AD. The currently approved drugs rivastigmine, galantamine, donepezil, memantine, and memantine combined with donepezil increase the amount of neurotransmitters in the brain and are palliative treatments only.[2]

Conclusion

There is no test currently available that has the ability to rule in, or rule out, an increased risk of developing Alzheimer's disease in later life. A safe, cost-effective and simple blood test would help diagnose people at risk of or who already have symptoms of Alzheimer's disease. In many cases this would negate the need for costly PET imaging. While there are a number of ongoing studies into new therapies, so far no medical treatments have been able to cure or slow the advance of Alzheimer's disease.

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