Alzheimer's Disease: An Overview of the Pathophysiology, Genetics, and the Search for a Cure

Introduction

Description

Alzheimer's disease (AD, Alzheimer's) is a common neurodegenerative disease and the most common cause of dementia.[1, 2] It is characterized by decreased mental function and instability that gradually worsens with time. Symptoms generally begin with mild psychological abnormalities, with a decreased ability to think and remember. Examples include forgetting the location of objects; short term memory loss; and difficulty planning or organizing everyday activities.

As the disease progresses, symptoms become more pronounced. Patients may experience mood swings, personality changes, being unable to remember one's own personal details, confusion about time and day, and a tendency to wander and become lost. In its final stages, patients with AD typically need constant monitoring and help performing basic tasks. Physical symptoms set in, such as difficulty walking, swallowing, and an increased susceptibility to infection.[7] Most people with AD die from a secondary infection.[2]

Over 90% of people who develop Alzheimer's begin to show symptoms after ages 60-65, after which the disease is considered to be late onset Alzheimer's disease (LOAD). Early onset Alzheimer's disease (EOAD) patients develop symptoms before age 65. Symptoms of AD are usually consistent regardless of the age at onset.[9]

Pathophysiology

Alzheimer's disease is associated with the formation and accumulation of structures in the brain known as amyloid-beta (Aβ) plaques and neurofibrillary tangles.[21] The precursor to the amyloid-beta protein, Amyloid Precursor Protein (APP), is a transmembrane protein found on neurons that is involved with cell growth and repair. Over time, APP can be cleaved by several enzymes, one of which includes β-secretase. After β-secretase cleaves most of the extracellular portion of APP, γ-secretase can cleave off the intracellular portion, leaving the middle section of the protein, amyloid-beta. Amyloid-beta molecules can adhere to other amyloid-beta molecules, forming agglomerations known as amyloid-beta plaques, which can disrupt normal cell function by blocking synapses and affecting ion transport into and out of the neuron.

Neurofibrillary tangles are formed by tau proteins, which help stabilize microtubules inside neurons.[21] Over time, tau proteins can become malformed or dislodged, and form tangles with each other. These tangles have no biological use and the involved tau proteins no longer facilitate nutrient transfer

along the microtubules. Macro-scale neurophysiological changes that occur in the late stages of the disease include atrophy of the brain, decreased cortical mass, and increased ventricular volume.

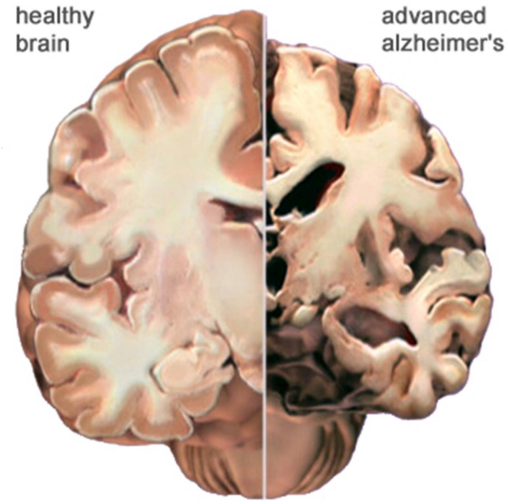

Figure 1. Coronal cross-section of a healthy brain (left) and a brain with advanced AD (right). The brain from the AD patient has significant atrophy, lower hippocampal volume, increased ventricular size, and shrunken gyri.[4]

Epidemiology

Alzheimer's disease affects around 20-24 million people worldwide, with cases more concentrated in developed countries (which typically have longer life expectancies), such as the United States.[1, 19] The number of people diagnosed with AD is increasing rapidly as the population ages. The majority (>90%) of cases are late-onset, beginning after age 65. LOAD occurs with a somewhat higher frequency in females versus males, even after adjusting for differences in life expectancy; the reasons for this have yet to be ascertained.[10] Compared with Caucasians, Hispanics are about 1.5 times as likely to develop AD past age 65, and blacks are about twice as likely to develop it.[20]

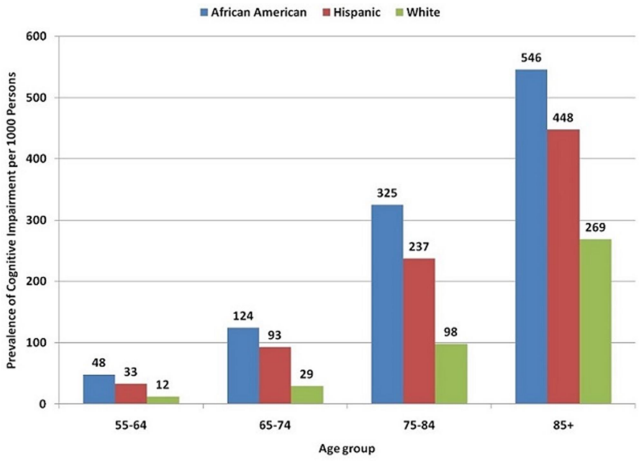

Figure 2. The prevalence of cognitive impairment, including dementia, among different races by age. A consistent trend shows that blacks are more likely to be cognitively impaired as they age as compared with whites, with Hispanics having impairment rates between the two.[20] (HHS)

Genetic Basis

Early Onset

Early onset Alzheimer's disease cases comprise about 5-10% of all Alzheimer's diagnoses. For EOAD cases with a known genetic component (~15%), the disease is typically associated with mutations in one of three genes, two of which are on chromosome 1 (presenilin 1) or chromosome 14 (presenilin 2) that regulate gamma-secretase activity.[9] Symptoms from presenilin-derived Alzheimer's disease typically arise around age 30, and the diseases follow an autosomal dominant pattern. While uncommon, mutations in the third gene, the APP gene itself (chromosome 21) has been associated with AD. Alzheimer's disease from these three sources are collectively referred to as familial Alzheimer's disease (FAD).

People with trisomy 21 (Down's syndrome) almost always start showing symptoms of Alzheimer's by age 40; it is thought that the additional copy of the APP gene increases the chance that plaques will be formed in these patients. However, trisomy 21 accounts for less than 1% of all Alzheimer's cases.[6, 10]

Late Onset

Late onset Alzheimer's disease accounts for 90-95% of all Alzheimer's cases. The causes and risk factors of LOAD are not well understood but are being intensively studied.[9, 10, 11] While there have been some genetic and environmental associations identified with LOAD, most cases cannot be fully explained by specific causes; therefore, almost all cases are characterized as sporadic. A large number of genome-wide association studies (GWAS) have been performed to attempt to identify loci, commonly SNPs, that are correlated with AD risk.

GWAS study

In a *JAMA Neurology* study, Naj, et al. performed a genome-wide association study to determine the effect, if any, of minor alleles (MA) at specific loci on the age at onset (AAO) of Alzheimer's disease.[3] Previous GWAS studies have associated LOAD with many genetic variants; to verify that some of these loci affected the risk of developing LOAD, this study examined the effect of the ten most strongly associated variants ($p < 5.0 \times 10^{-8}$) on the AAO phenotype, which included 9 SNPs and the APOE-4 (Apolipoprotein E) ε4 haplotype. In this study, 9162 Caucasian individuals with LOAD (AD diagnosed after age 60) that had full AAO information were genotyped using Illumina/Affymetrix GWAS high-density SNP microarrays. Any SNP with a minor allele frequency (MAF) of less than 0.01-0.02 was not analyzed due to the associative limitations conferred by the study sample size. After performing regression association analyses on the data set, the study found that four of the ten alleles were significantly associated with lower AAO for LOAD ($p < 0.005$; corrected for multiple comparisons): the CR1, BIN1, and PICALM SNPs, along with APOE-4. As expected, the presence of APOE-4 was most strongly associated with lower AAO, with an average AAO change of -2.45 years ($p = 3.3 \times 10^{-96}$). The other three SNPs with statistically significant AAO associations each individually decreased AAO by an average of 3-6 months (See β values in *Figure 3*).

					Age at Onset						LOAD Risk	
					Minimal Adjustment Model			Extended Adjustment Model				
SNP	CH:MB	Nearest Gene	Minor Allele	MAF	β (95% CI)	*P* Value	*P* Value for Het	β (95% CI)	*P* Value	*P* Value for Het	OR (95% CI)	*P* Value
rs6701713	1:207.8	*CR1*	*A*	0.24	−0.41 (−0.65 to −0.17)	7.2×10^{-4}	.405	−0.41 (−0.69 to −0.12)	4.9×10^{-3}	.422	1.16 (1.11 to 1.22)	4.6×10^{-10}
rs7561528	2:127.9	*BIN1*	*A*	0.37	−0.31 (−0.52 to −0.09)	4.8×10^{-4}	.855	−0.32 (−0.57 to −0.08)	9.9×10^{-3}	.684	1.17 (1.13 to 1.22)	4.2×10^{-14}
rs9349407	6:47.5	*CD2AP*	*C*	0.32	−0.03 (−0.25 to 0.19)	.765	.266	−0.14 (−0.40 to 0.11)	.273	.860	1.12 (1.07 to 1.18)	1.0×10^{-6}
rs11767557	7:143.1	*EPHA1*	*C*	0.18	0.03 (−0.26 to 0.32)	.830	.861	0.07 (−0.24 to 0.39)	.659	.657	0.87 (0.83 to 0.92)	2.4×10^{-7}
rs1532278	8:27.5	*CLU*	*T*	0.37	0.05 (−0.18 to 0.28)	.661	.137	0.0038 (−0.26 to 0.27)	.977	.108	0.89 (0.85 to 0.93)	8.3×10^{-8}
rs4938933	11:60.0	*MS4A4A*	*C*	0.36	0.09 (−0.14 to 0.31)	.448	.454	0.018 (−0.23 to 0.27)	.887	.584	0.88 (0.85 to 0.92)	1.7×10^{-9}
rs561655	11:85.8	*PICALM*	*G*	0.38	0.33 (−0.12 to 0.55)	2.2×10^{-3}	.915	0.32 (0.07 to 0.57)	.011	.957	0.87 (0.84 to 0.91)	7.0×10^{-11}
rs3752246	19:1.1	*ABCA7*	*G*	0.34	−0.27 (−0.55 to 0.02)	.064	.700	−0.19 (−0.51 to 0.13)	.242	.748	1.15 (1.09 to 1.21)	5.8×10^{-7}
Haplotype rs7412/ rs429358	19:45.4	*APOE*	ε4	0.35	−2.45 (−2.68 to −2.21)	3.3×10^{-96}	.094	−0.24 (−0.75 to 0.27)	.360	.874	3.02 (2.86 to 3.20)	2.2×10^{-320}
rs3865444	19:51.7	*CD33*	*A*	0.20	0.10 (−0.13 to 0.33)	.377	.596	0.13 (−0.13 to 0.38)	.338	.872	0.89 (0.86 to 0.93)	1.1×10^{-7}

Figure 3. Results of the analysis of the effect of 10 loci minor alleles (MA) on LOAD AAO in 9162 AD patients. β represents the average AAO change associated with each MA. CR1, BIN1, PICALM, and APOE MAs showed statistically significant reductions in AAO with the multiple hypothesis testing threshold of $p < 0.005$. After adjusting for the effect of APOE-4, CR1 and BIN1 maintained their statistical significance.[3]

Apolipoprotein E

Apolipoprotein E is primarily a cholesterol transporter and is involved with clearing amyloid-beta fragments from the brain. There are three major variants of the APOE gene: E2, E3, and E4, with each variant conferring a single amino acid difference. E3 is the most common variant and seems to have no effect on LOAD. E2 is the rarer variant and may have a protective effect against AD. The E4 variant is found in about 15-25% of all humans and is strongly associated with an increased chance of developing AD, as well as a lower AAO. Having one copy of E4 increases the lifetime risk of developing AD by 3-5 times, with two copies associated with an increased risk of 9-20 time. It is thought that the increased risk is due to Apolipoprotein E4's inferiority in clearing away amyloid beta fragments.[15]

Complement Receptor 1 eQTL

The CR1 gene, located on chromosome 1, codes for complement receptor 1. CR1 is involved in regulating the complement cascade of the immune system and the clearing of debris from cells, such as amyloid-beta fragments.[22] Variations at the CR1 locus have been associated with an increased risk of developing Alzheimer's disease and lower AAO. For example, the GWAS study referenced above found that a SNP about 200 kilobases away (*trans*-acting) from the CR1 gene was associated with reduced AAO. The exact molecular mechanisms that cause changes in AD presentation are not known.[23]

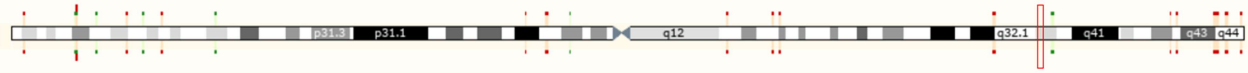

Figure 4. The location of the CR-1 gene on chromosome 1 (red box).[17] The gene is located at base pairs 207,496,147 to 207,640,647. CR-1 modulates the immune complement cascade and waste removal. Variations around the CR-1 locus have been associated with AD risk. (Ensembl archive)

Non-genetic Factors

While AD has many genetic components, it is a complex disease with many contributing environmental and lifestyle factors. The chief non-genetic factor behind AD is age.[18, 19, 20] Most cases of AD occur in people over the age of 65, with the chances that a person will develop AD increasing rapidly after that point. Other risk factors include poor diet, high blood pressure, and obesity. Higher education levels seem to be associated with a lower risk of developing AD; it has been hypothesized that more education increases the density of the synapse network in the brain, making it more resilient to damage, but the exact reason is not certain. More recently, traumatic brain injury has been studied as a possible risk factor in AD, especially for people who have the APOE-4 allele or other risk factors, but more research is needed to confirm a causal link.[24]

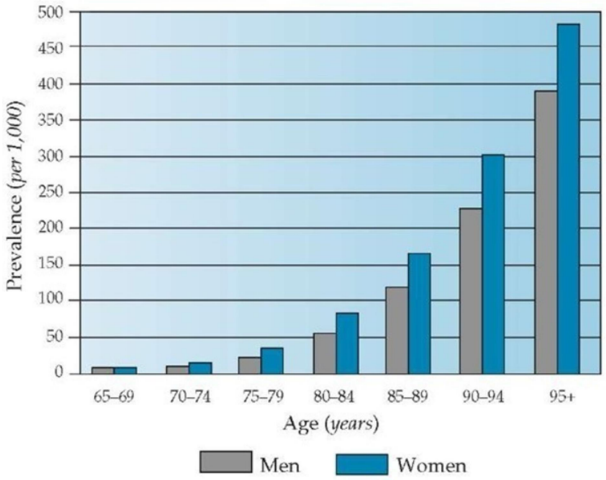

Figure 5. Prevalence of Alzheimer's Disease per 1000 people in the United States by age and gender.[14] (American Psychiatric Association)

Treatment and Prevention

Alzheimer's disease currently has no cure, and current medication regimens are ineffective in many patients.[6] Many studies are underway that are attempting to block the formation or deposition of amyloid-beta plaques by targeting amyloid-beta with antibodies.[25] Currently, the NIH Dominantly Inherited Alzheimer's Network (DIAN) is investigating whether certain antibodies, when administered pre-symptomatically, can change the AAO or progression the AD in patients with certain genetic changes that nearly guarantee that they will develop EOAD. Another study that was finalized in 2014 analyzed the effect of a monoclonal antibody, Solanezumab, on AD outcomes in a Phase III clinical trial.[5] Solanezumab was designed to target the central domain of amyloid-beta fragments and reduce their deposition in the brain; a detailed description of the study is included in the final section.

Historical Background

For most of history, dementia was considered a natural part of aging. Alzheimer's disease was first described by German psychiatrist Alois Alzheimer in 1907, after whom the disease is named. Alois

studied a woman in her mid-50s who had severe cognitive impairments and memory problems. After her death, he performed an autopsy on her brain and noticed unusual lesions, which are now known to be amyloid-beta plaques and neurofibrillary tangles. Soon, it became generally accepted that these abnormal structures played a central role in Alzheimer's disease.[27]

Before the genomic era, the familial form of Alzheimer's disease (FAD) offered the most promising genetic path to identify the genes causing the disease. Because amyloid beta-protein had been found in the core pathology markers (senile plaques and the neurofibrillary tangles) in patients with Alzheimer's disease, it was thought that the genes causing Alzheimer's disease had to be directly related to amyloid beta-protein. However, in a 1987 *Nature* study, this assumption was overturned. In this study, Tanzi, et al. hypothesized that if the Aβ protein gene causes familial Alzheimer's disease (FAD), then the pattern of segregation of the Aβ gene in FAD pedigrees would be very similar. Using separation and analysis of restriction fragment length polymorphisms (RFLPs) as markers to conduct classical linkage analysis in 4 pedigrees, the study showed that there were essentially no linkage signals, making it unlikely that the Aβ gene is causal to FAD. This was later on proven correct as other genes were found to be causal to FAD.[28]

Current Standard of Diagnosis

Alzheimer's disease symptoms are very similar to those of other dementias, so diagnosing it correctly can be challenging. Currently, the only method to definitively identify a case of Alzheimer's is to perform a tissue analysis post-mortem, which is not applicable in most cases. Generally, diagnosis involves mental status and cognitive testing, behavioral function assessment, neurological and physical examinations, and examining a patient's family history and genetic predisposition for Alzheimer's (if available). Doctors typically also attempt to rule out other conditions, such as depression or Parkinson's disease, and other forms of dementia. Several indexes to assess cognitive function are used; one common examination is the Alzheimer's Disease Assessment Scale (ADAS). Brain imaging using MRI, CT, or PET (Positron emission tomography) may be used to identify changes consistent with AD, and rule out brain hemorrhages and other specific abnormalities. The combination of these tests is usually, but not always, sufficient to make a diagnosis. Research with PET scans is underway to determine whether they can be used to detect tau protein tangles or amyloid beta plaques.[26] These PET approaches may enable direct diagnosis of AD.

Clinical trial: Solanezumab

Solanezumab is a monoclonal antibody designed to target amyloid-beta fragments and prevent them from clumping or being deposited in the brain. Phase I and Phase II trials with solanezumab indicated that it could have had the effect of effluxing amyloid-beta from the cerebrospinal fluid (CSF) into the blood. In the *Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease,* two double blind, randomized studies were performed on two groups of otherwise healthy patients aged 55 years or older who had mild or moderate AD. The studies, termed Expedition 1 and Expedition 2, each had about 1000 patients, half of whom were randomized to receive either solanezumab or placebo. The severity of Alzheimer's in each patient was determined by three primary indexes: the 11 or 14 item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-11 [scale 0-70] or ADAS-14 [scale 0-90]), and the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL [scale 0-78]), with higher scores on each scale indicating greater cognitive impairment. Patients in

each study were given the mental assessments, then treated with 400mg of solanezumab via 70 mL intravenous infusion over 30 minutes, every 4 weeks for 18 months. Follow-up mental assessments were performed at week 80, at the conclusion of the treatment course. The difference between each patient's baseline (week 0) and post-treatment (week 80) score was calculated and averaged within their respective groups.

The study found no clinically significant difference between the placebo group and the solanezumab group in either study. The changes in baseline and final scores on each of the three primary measures were similar in both the placebo and drug groups; the result for both studies, and the trial as a whole, was negative.[5] While the mechanism of this compound was exciting and promising, additional efforts from basic neuroscience, genetics and clinical studies are needed to identify effective treatments to achieve a cure for AD.

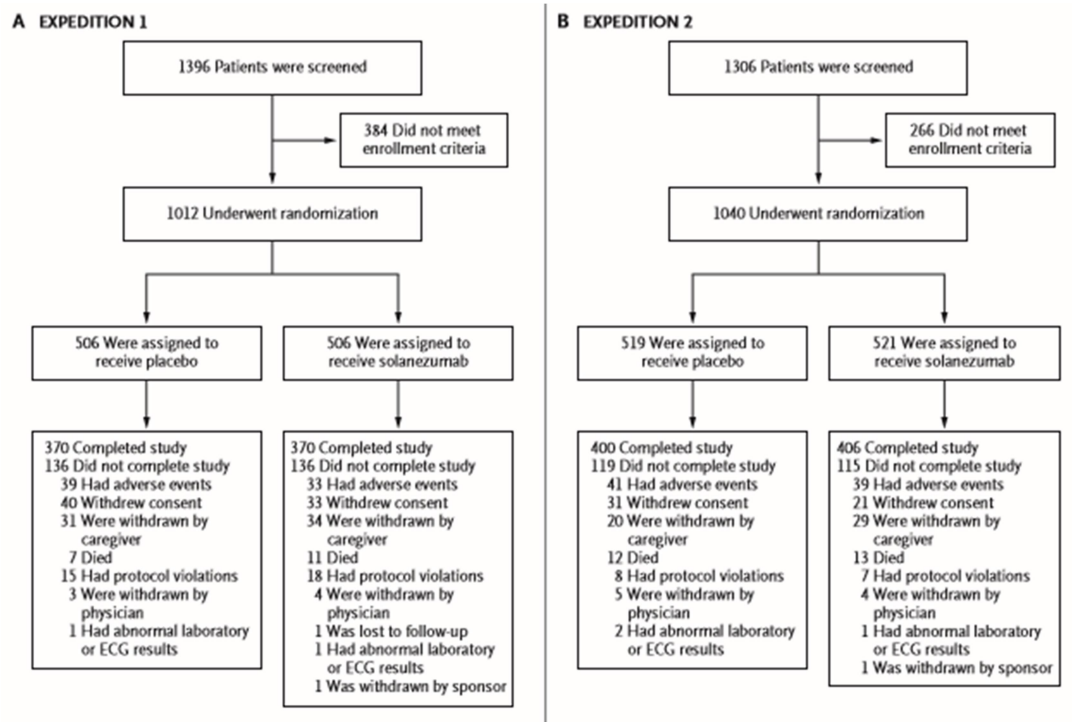

Figure 6. Flowchart of the trial design for each expedition. Each study randomized around 1000 eligible, otherwise-healthy AD patients aged 55 or older to placebo or solanezumab. The number of patients that completed the study in each group, as well as the causes that some patients did not, are listed. The difference cognitive test scores for each group before and after treatment were recorded, averaged, and analyzed. Note the similarity in the completion statistics of each placebo versus drug group; it can be inferred that the action of the drug was minimal.[5]

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