International Research Journal of Advanced Engineering and Science
ISSN (Online): 2455-9024

Statistical Interpretation on Alzheimer's Disease

Juhwan Suh
Department of the Neuroscience, Johns Hopkins University, Baltimore, Maryland, United States, 21287
Email address: spfhapfhty@gmail.com

Abstract*— *The cause of Alzheimer's is neuronal cell death. However, there is no cure to prevent neuronal cell death in advance. Health care strategies are essential to prevent aging of neuronal cells. Significant differences in the incidence of Alzheimer's disease by race, region, and gender have not yet been reported. When future medical care is realized, early detection of Alzheimer's disease is possible and pre-emptive treatment is achieved. The age of healthy aging without Alzheimer's disease is approaching.

Keywords*— *Alzheimer's disease(AD), Amyloid-beta, Tau protein, Creutzfeldt-Jakob disease (CJD).

I. INTRODUCTION

By the year 2050, one out of 85 people around the globe is expected to suffer from cognitive impairment arising from alzheimer's disease. South Korea is not an exception; baby boomer generation is soon to reach the threshold age 65. People are burdened with gigantic medical cost from alzheimer's disease, not to mention the emotional devastation when they see their beloved people lose their bright minds. However desperate the cure for alzheimer's disease is needed, pharmaceutical giants have started to give up on finding alzheimer's disease treatment. Although tremendous amount of research funding has been, and still is, invested for alzheimer's disease, the cause of such devastating disease is still vague. This research paper includes statistical interpretation of the epidemiology of alzheimer's disease to predict the factors that might affect the chance of developing alzheimer's disease, symptomatic signs of alzheimer's disease by its stage, updated hypotheses for the cause, and description about the mechanism of currently available drugs as well as promising strategies to develop treatment. Statistical interpretation categorized the patients under several criteria: (1) Gender, (2) Ethnicity, (3) Race. Next, three hypothetical causes of alzheimer's disease's pathogenesis, (1) amyloid hypothesis, (2) cholinergic hypothesis, (3) tau protein hypothesis are explained in order to evaluate probable method pharmaceutical researches should investigate. In following chapter, Alzheimer's Disease's symptoms were categorized by their stages. Overview of current hypotheses about AD's pathogenesis, mainly sporadic AD is discussed in chapter IV. Each of hypothesis's strengths and weaknesses would be further mentioned. In chapter V, Current AD treatment and prospective medications are briefly mentioned. In the last part of the document, conclusion.

II. STATISTICAL INTERPRETATION

Gender: According to Alzheimer's Association's *2012 Alzheimer's Disease Facts and Figures*, women is much more likely to develop AD than men (1). This striking disparity between lifetime risks of men and of women might stem from hormone fluctuation women go through once they reach their 50s. Risk factors, such as insulin, systolic blood pressure, and cholesterol rate increased around the time of menopause. However, since systolic blood pressure and insulin level had been increasing steadily before the menopause, they are not necessarily caused by menopause but aging. Cholesterol rate, however, skyrocketed (2).

Age	Women	Men
65	17.2	9.1
75	18.5	10.2
85	20.3	12.1

Created from data from Seshadri et al. (1)

Fig. 1. Framingham Estimated Lifetime Risks for Alzheimer's by Age and Sex.

If early-onset AD patients' gender proportion is more even than that of older age, menopause could be one of the factor that contributes to the development of AD. If women's menopause and the following hormonal imbalance as well as increase in cholesterol rate attributes to the doubling of rate of men's, hormonal treatment to retain the body mechanism after menopause could help women avoid AD. Another possible factor that might cause the difference is education level. It has been believed, although for poorly understood, that participating in cognitively challenging activity, such as chess, can reduce the chance of getting AD. Studies show that females who are diagnosed with Alzheimer's Disease received fewer years of education (4.6±3.8 years) than men (7.6±4.5 years) (3); it can be presumed that less education which could possibly result in less social activity might be a contributing factor to women's higher likelihood of developing AD. However, limitation of the diagnostic test should be concerned. Measuring cognitive ability via a written test must pose more difficulty to illiterate, or individual who has less experience with education.

Ethnicity:

A. Africa

A number of studies lead Osuntokun and his colleagues to state that "No authentic case of AD has been reported in an indigenous black African". An investigation took on 1,122 individuals above the age 40, approximately one third of them over the age 65, but no serious case of dementia was reported. It seems to indicate that Nigerians are less prone to AD (4). However, follow-up investigation on African-American immigrants proved otherwise. Age-adjusted prevalence rates for dementia (2.29 percent) and AD (1.41 percent) among community-dwelling indigenous African elders were

Ju-hwan Suh, "Statistical Interpretation on Alzheimer's Disease," *International Research Journal of Advanced Engineering and Science*, Volume 2, Issue 2, pp. 343-349, 2017.

International Research Journal of Advanced Engineering and Science
ISSN (Online): 2455-9024

significantly lower than rates of dementia (8.24 percent) and AD (6.24 percent) among African Americans, those who are likely to share the same genetic lineage. Age-standardized annual incidence rates of dementia (1.35 percent) and AD (1.15 percent) were significantly lower in Ibadan than rates of dementia (3.24 percent) and AD (2.52 percent) among African Americans in Indiana (6). From the result, genetic factor does not play a role in Nigerian's relative low AD occurrence. This inconsistency in AD penetrance rate between might be the following: (1) Native Nigerian population's life expectancy is much shorter than that of African American, so Nigerian elderly who had the potential to develop AD later died from other reasons. (2) Detrimental environmental factors might affect negatively to the AD(3). Dietary adjustment in the United States could have led to increased chance of AD.

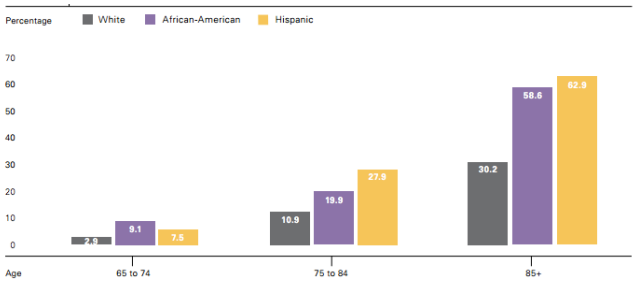
B. Asia

Rates of AD is lower among Asians than among Europeans, while overall rates of dementia is similar. It is because Asian populations more frequently have vascular dementia (7, 12). Higher rates of vascular dementia is partly because of less medical technics and diagnostic accuracy in Asian countries. Recently, this pattern started to change along with Asian countries' economic prosperity; decrease in vascular dementia has been reported (8). This improvement mirrors better control over cardiovascular risk factors, and increase in accuracy in diagnosis. Prevalence of AD has been increasing in Eastern Asia. Westernization of risk factors such as high-fat diet and lack of exercise is presumed to add up the chance of AD, so developing nations' AD rates are likely to exacerbate. Current data from developing countries suggest that age-adjusted dementia prevalence estimates in 65 year olds are high (≥5%) in certain Asian and Latin American countries, but consistently low (1–3%) in India and sub-Saharan Africa (47). This could be because of high mortality rate, or once again, difference in a diet. India has the largest number of vegetarians in the world. Vegetarians' main source of protein is soybeans, which contain by far the most amount of phytoestrogen(48). Phytoestrogen can mimic the human produced hormone estrogen(48), a female hormone whose deficiency causes women to be more predisposed to increase in cholesterol rate. In a similar fashion, the reason for low rates of AD among Asians when they followed their traditional diet pattern in the past could be their means of protein intake, since Asians used to rely on soybeans for protein instead of dairies and meat.

C. Europe

European's average rate of AD is much higher than that of Asian or African, while almost equal to American. This fact is only self-evident, considering that most of Americans are European descent who share similar westernized lifestyle (9). The Liverpool Health and Ethnicity Project (10) reported that the prevalence of dementia among a sample of 418 English-speaking elders with various ethnic backgrounds was comparable to that found among whites (2 to 9 percent). However, in this same study, the authors found that the prevalence of dementia among people who had the same ethnic backgrounds but whose native language was not English surged (21 to 27 percent). This result once again corroborates the limitation in cognitive measuring test. People who did not speak English were less likely to answer questions that involve much of their lingual ability, such as remembering their address (11).

Race:

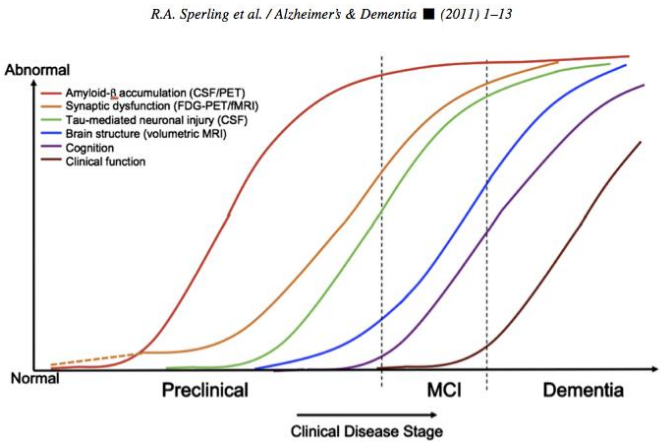


Created from data from Gurland et al. (17)

Fig. 2. Percentage of AD development among different races.

According to the 2012 Alzheimer's Disease Facts and Figures, blacks and hispanics had higher proportion of people suffering from AD than non-hispanic whites in the United States. While 10.9% of whites in the age range 75 to 84 had AD, the percentage bumped to 19.9% for blacks and 27.9% for Hispanics (13). This recalls several possible factors that can lead to more likelihood of getting AD. First, blacks and hispanics average household income is significantly lower than non-hispanic whites. Affordability of medical care would favor non-hispanic whites, who are economically stable than the other two races in general. The other reason, much of hispanic origins use Spanish as their mother tongue. The phenomena noted from the Liverpool Health and Ethnicity Project, of which people who did not speak English had problems with answering questions, might have affected the experiment result in a similar fashion.

III. Symptoms of Alzheimer's Disease by Stage



Copied from R. A. Sperling et al. Alzheimer's & Dementia (18)

Fig. 3. Changes in a patient's body in accordance with AD progress.

Pre-dementia:

Amyloid-beta accumulation starts on preclinical stage before synaptic dysfunction, neuronal injury, and brain

Ju-hwan Suh, "Statistical Interpretation on Alzheimer's Disease," *International Research Journal of Advanced Engineering and Science*, Volume 2, Issue 2, pp. 343-349, 2017.

structure transformation (16). It takes approximately eight years until a person who started to have mild cognitive difficulties to clinically diagnosed as AD (14). Early symptoms could be commonly mistaken as a mere forgetfulness, yet still affect daily activities. Memory loss is the most prevalent example. An individual will have difficulty remembering recently learned facts and struggle to acquire new information. Family members and close friends might notice subtle change in personality. Apathy, depression, abnormal fluctuation in emotional state, irascibility are all possible signs of AD. Language problem emerges along with other symptoms. While conversation, a person might repeat himself, forget the topic of the dialogue, or have a trouble coming up with a vocabulary, such as referring a "watch" as a "hand clock"(15). Preclinical stage, one does not need a caregiver in general. He might have troubles carrying out daily activities, but cognitive impairment is relatively mild.

Early:

By early stage, people with AD's cognitive ability is impaired enough be diagnosed. Difficulties with language, perception (agnosia), execution of movements (apraxia) are possible to occur. Although memory loss are prominent problems for most of AD patients, older memories and implicit memories (memory related to movements, such as riding a bicycle) are less affected than newly learned facts or recent memories (19).

As language problems worsen, the person with AD would recede from society. Frustrated by less fluency and fewer vocabulary themselves, less communication results, though the person with AD can express their ideas to enough extent (19). People with AD on this stage can continue daily tasks without big problems, but might need help with cognitively demanding activities (19).

Moderate:

As the disease progresses, patient has to rely on a caregiver. Using inappropriate words during the conversation becomes severe, so speaking and writing ability declines to a serious degree. Patient loses ability to carry out complicated physical movements, such as riding a bicycle or using chopsticks. Long term memory starts to be impaired, so patient might fail to recognize kins and close friends (19). From this stage, caregiver's role becomes much more burdensome. Emotional instability and change in personality—irritability, crying, outburst of unpremeditated aggression, or resistance to caregiving—can be very stressful. Delirium and other delusional symptoms begins, and patient lose the ability to understand his cognitive problems and disease process (anosognosia) (19). About one third of the people with AD develop illusionary misidentifications, such as trying to feed a pillow as if it were his child (19).

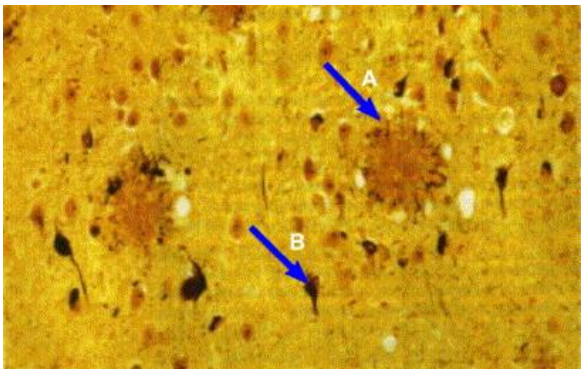
Families and caretakers choose to move the patient to nursing home, or long term care facilities because of the stress (19,20).

Advanced Stage

Language is almost lost except for a few short phrases. Some shows complete apathy, while others, aggressiveness. AD ultimately drives a person to be completely dependent on caregiver's help, as a patient can't walk or eat without assistance (21). Patient forgets if he is hungry or thirsty, so it is caregiver's duty to either encourage him eat or feed him (21). As the patient becomes chair-bound or bed-ridden, he is more susceptible to infection such as pneumonia (19). It is usually not AD itself that kills the patient, but the infection that a patient can't fight off easily (19).

IV. Hypothesis for Pathogenesis of AD

Amyloid Hypothesis :



Crentsil, Victor (46)

Fig. 4. (A) Amyloid plaque, (B) Neurofibrillary tangle.

Amyloid hypothesis pinpoints the accumulation of Amyloid beta or Abeta, commonly represented as Aβ, the cause of neurofiber tangles and eventual degeneration of brain ability among AD patients (25). Abeta's physiological role is yet to be unraveled; some evidence shows Abeta lacks functional value (31), while the other supports otherwise (32, 33).

Abeta is cleaved from APP, *Amyloid Precursor Protein*, by beta-secretase and gamma-secretase. (22) APP is located on chromosome-21. Scientists postulates the reason Down Syndrome patients developing AD invariably after certain age is because those have extra copy of chromosome-21 (25). Unbalanced proportion of APP is seemingly linked with AD. Another genetic factor that supports amyloid hypothesis is the fact that people with APO-E4 has more likelihood of developing AD (25). APO-E4 is a specific isoform of apolipoprotein that controls the breakdown of Abeta (29). Among various forms of apolipoproteins, APO-E4 is one of the less efficient types. Individuals who are homozygous for APO-E4 allele are predisposed to develop alzheimer's, and heterozygous individuals, too, to a less degree (29). New research results are trying to build a link between insulin and Abeta. Epidemiological studies and clinical evidence have been showing proportional relationship between hyperinsulinemia (excess level of insulin circulating in blood) as well as type 2 mellitus diabetes(high blood glucose along with low insulin level) and AD (34). Possible mechanism behind the increased chances of being affected by AD is Insulin Degrading Enzyme (IDE) (34). Insulin and Abeta are both substrates of IDE, and share similar amino acid sequence (34). Also, abnormal glucose utilization tends to be part of AD pathology (25). Some claims that Abeta and insulin competes for IDE (23). If plenty of insulin does not leave enough IDE to degrade Abeta, it will eventually accumulate and lead to

Ju-hwan Suh, "Statistical Interpretation on Alzheimer's Disease," *International Research Journal of Advanced Engineering and Science*, Volume 2, Issue 2, pp. 343-349, 2017.

amyloid plaque in brain cells. Clinical trials to eliminate the senile plaque itself could not stop neurodegeneration. And so, more recent research results suspects amyloid-derived diffusible ligands (ADDLs), instead of senile amyloid plaque, as fundamental cause of AD (29). Neurotoxic amyloid oligomers are believed to lead to mitochondrial dysfunction in neurons. Experimental results have shown that ADDLs lead to serious impairment in both anterograde and retrograde transport of mitochondria along axons (29). Recently, experimentation on transgenic mice showed microinjection into living rats of human-produced Abeta showed that ADDLs alone can inhibit long term potentiation in the hippocampus, which is required for memory formation (24). Although Amyloid Hypothesis provides the most compelling explanations, some critics cast doubt (25). While early onset AD patients fit to the amyloid hypothesis, sporadic AD patients mostly lack genetic factors. Statistically, less than 5-10 % of Alzheimer's cases are early onset, and only 13 % of the early onset cases fall under familial Alzheimer's (35). More, the most frequently voiced objection is that the number of amyloid deposits in the brain does not correlate well with the degree of cognitive impairment that the patient goes through. Amyloid hypothesis supporters nevertheless points out the degree of dementia symptoms correlates well with the concentration of soluble amyloid instead of the number of plaque counts assayed histologically(25). Another objection comes from the experiment result that transgenic mice undergoing progressive Abeta deposition often do not show clear cut neuronal loss (41).

Cholinergic hypothesis:

Cholinergic hypothesis postulates the reduction of neurotransmitter synthesis, especially Acetylcholine, is the fundamental cause of AD (42). In antithetical sense, early researchers developed medications that inhibits esterase (enzyme that breaks down acetylcholine) so that synapse would respond to relatively weaker signals (44). Prescribed alzheimer medications such as Razadyne® (galantamine), Exelon® (rivastigmine), and Aricept® (donepezil), rely on this mechanism (44). However, since neurotransmitter's synthesis gradually decline, AD medication's pharmaceutical benefit is only ephemeral and palliative; it cannot reverse the progress, nor can it deter (25). Cholinergic hypothesis has been losing its ground for support, because researches have proven that bolstering the production of neurotransmitter fails to help an AD patient's symptoms (25). It also does not give successful explanation for amyloid plaque buildup, as well as tau protein neurofibrilliary tangles (25).

Tau hypothesis:

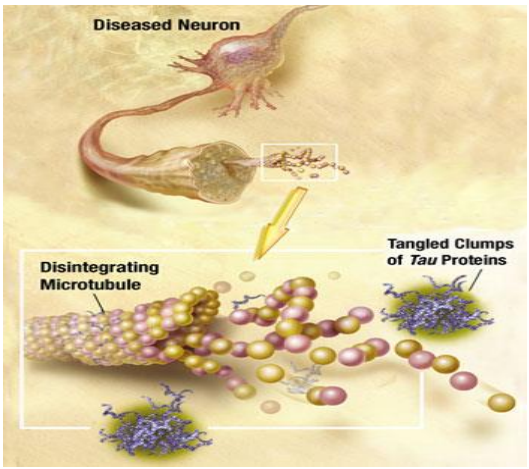
Tau hypothesis points abnormal tau protein is the linchpin of the AD cascade. Tau protein is a phosphoprotein, whose main function is stabilization of microtubules in neuronal cells(40). AD patient's tau proteins are three-fold greater than normal brain tau, and those proteins form aggregates of paired helical filament form(25). Hyperphosphorylation of tau protein (pTau) results neurofibrillary tangles inside neuronal cells, causing fiasco within microtubule system(25). However, recent findings lead to the conclusion that accumulation of hyperphosphorylated tau protein comes after the changes in APP processing and Abeta deposition. Mutations in tau protein causes accumulation of neurofibrillary tangles, but not amyloid plaques in the brain (25). Although pTau causes severe neuronal damages—frontotemporal dementia with parkinsonism tantamount to Alzheimer's, abnormal deposition of tau protein comes after the initiation of AD(18). Also, an individual from an Australian family with spastic paraparesis variant of familial AD died before the onset of dementia symptoms; posthumous autopsy showed she had plenty of amyloid deposition but no neurofibrillary tangles (25).

Disease	Etimology	Regions affected	Pathology	Related proteins
Alzheimer's Disease (AD)	Sporadic (ApoE risk factor)	Cortex, hippocampus, basal forebrain, brain stem	Neutric plaques and neurofibrillary tangles	Abeta peptide from APP, hyperphosphorylate-d tau protein
	Amyloid Precursor Protein (APP) (dominant)	Same as sporadic	Same as sporadic	Same as sporadic
	Secretases (prenesilin 1,2)	Same as sporadic	Same as sporadic	Same as sporadic
Frontotemporal dementia with Parkinsonism	Tau mutation	Frontal, temporal cortex	Pick bodies	Hyperphosphorylate-d tau protein

Created from C. A. Ross, et al. (39)

Fig. 5. Comparison between AD and frontotemporal dementia with Parkinsonism.

The density of formed aggregates within the neuronal system correlates with dementia. Even if tau hypothesis is proven wrong as the underlying reason of AD pathology, it is still a good target of further research for pharmaceutical development (25).



Neurofibrillary tangle formed by hyperphosphorylated tau protein causing microtubules disintegrate
Cooper, Paul (45)

Fig. 6. Neurofibrillary tangle.

Prion Hypothesis:

Recently, scientists started to suspect prion for AD pathogenesis. Prion, misfolded malignant protein that further

Ju-hwan Suh, "Statistical Interpretation on Alzheimer's Disease," *International Research Journal of Advanced Engineering and Science*, Volume 2, Issue 2, pp. 343-349, 2017.

International Research Journal of Advanced Engineering and Science
ISSN (Online): 2455-9024

causes other proteins to malfunction like itself, had been known as infectious agent of Creutzfeldt-Jakob disease and many other neurodegenerative diseases (39). Creutzfeldt-Jakob disease (CJD) and Alzheimer's disease (AD) are neurodegenerative diseases that both share some important characteristics; they show accumulation of amyloid, prion protein PrP and Abeta respectively. Also, inflammation-related proteins such as complement factors, acute-phase protein, pro-inflammatory cytokines and clusters of activated microglia are concentrated near the amyloid deposits (39).

Disease	Etimology	Regions affected	Pathology	Related proteins
Alzheimer's Disease (AD)	Sporadic (ApoE risk factor)	Cortex, hippocampus, basal forebrain, brain stem	Neutric plaques and neurofibrillary tangles	Abeta peptide from APP, hyperphosphorylated tau protein
	Amyloid Precursor Protein (APP) (dominant)	Same as sporadic	Same as sporadic	Same as sporadic
	Secretases (prenesilin 1,2)	Same as sporadic	Same as sporadic	Same as sporadic
Prion disease (CJD, Kuru, fatal familial insomnia)	Sporadic, genetic, infection	Cortex, thalamus, cerebellum, other areas	Amyloid deposits, Spongiform degeneration	Prion protein

Created from C. A. Ross, et al. (39)

Fig. 7. Comparison between Prion disease and AD.

Although prion hypothesis has not gone through enough advancement in experiment to validate its ground, there were lots of cases that showed the coexistence of CJD and both sporadic and early-onset AD (37). Recently in Austria, 28 year old man who was confirmed of CJD also had Alzheimer-type senile plaques and cerebral amyloid angiopathy in widespread areas of the brain (38). Different from most of early onset AD cases, he lacked family history of AD, CJD, or any other neurological disease, and genetic mutations of the prion protein, presenilin 1 and 2, or amyloid precursor protein genes (38). The case is expected to give some clues about the pathology of CJD as well as AD.

V. Treatment Targets

Inhibiting Esterase:

Currently available prescription drugs for AD patients are only palliative; it inhibits the esterase, which degrades neurotransmitter acetylcholine, so that the neuronal transmission can be continued with reduced quantity of neurotransmitter (35). Some drugs like galantamine stimulates nicotinic receptors to release more neurotransmitter (35). However, as the synthesis of neurotransmitter gradually declines, efficacy of pharmaceutical treatments plummets. Memantine, Galantamine, Rivastigmine, Donepezil relies upon this mechanism (30). Common side effects are dizziness, constipation, headache for memantine; loss of appetite, vomiting, diarrhea, nausea, weight loss for galantamine; nausea, vomiting, muscle weakness, diarrhea, weight loss, for exelon; vomiting, nausea, diarrhea for donepezil (30).

Namenda® (memantine)	N-methyl D-aspartate (NMDA) antagonist prescribed to treat symptoms of moderate to severe Alzheimer's	Blocks the toxic effects associated with excess glutamate and regulates glutamate activation	Dizziness, headache, constipation, confusion
Razadyne® (galantamine)	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's	Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain	Nausea, vomiting, diarrhea, weight loss, loss of appetite
Exelon® (rivastigmine)	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's	Prevents the breakdown of acetylcholine and butyrylcholine (a brain chemical similar to acetylcholine) in the brain	Nausea, vomiting, diarrhea, weight loss, loss of appetite, muscle weakness
Aricept® (donepezil)	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate, and moderate to severe Alzheimer's	Prevents the breakdown of acetylcholine in the brain	Nausea, vomiting, diarrhea

Retrieved from Alzheimer's Disease Education and Referral (ADEAR) Center, A Service of the National Institute on Aging (30)

Fig. 8. Current Alzheimer's disease drug and its side effects.

Inhibiting Secretases:

Amyloid hypothesis postulates Abeta, cleaved from APP by beta-secretase and gamma-secretase, as the culprit of AD pathogenesis (25). And so, controlling secretases would inhibit the production of Abeta (29). In case of beta-secretase, medical researchers are trying to find small molecule inhibitor that would compete APP for the active site (25). Challenge is that the molecule has to fit the large active site of secretase, while being able to penetrate the blood-brain barrier (25). For gamma-secretase, various compounds have been developed to control its cleavage mechanism. One of them, Tarenflurbil was designed modulate gamma-secretase by Myriad Genetics (28). However, the company concluded the drug is ineffective in 2008 after phase III clinical trial. It is now believed its reasons of failure are weak pharmacological activity as an Abeta lowering agent and its poor brain penetration (28).

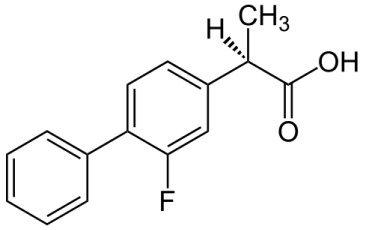


Image retrieved from Drug Discovery Opinion (45)

Fig. 9. Chemical structure of Tarenflurbil.

Ju-hwan Suh, "Statistical Interpretation on Alzheimer's Disease," *International Research Journal of Advanced Engineering and Science*, Volume 2, Issue 2, pp. 343-349, 2017.

Preventing the Oligomerization of Abeta:

This approach is exemplified by the use of active or passive Abeta immunization, in which antibodies to Abeta decrease cerebral levels of the peptide by promoting microglial clearance and by redistributing the peptide from the brain to the systemic circulation (25). This immunotherapy executed on transgenic mice achieved success, so human trials (AN-1792) seemed promising (25). Unfortunately, in 2002 Phase II trial, 6% of the experiment group developed so serious inflammation that the trial was stopped (27). Autopsies of individuals found that immunotherapy was effective in eliminating amyloid plaques, although it did not contribute to neurodegeneration. A modified version of AN-1972, ACC-001, is on its phase II trial. It aims to avoid T-cell activation, preventing activation of autoimmune system (27).

Modulating cholesterol homeostasis:

Although the reason is still vague, there has been epidemiological evidence that chronic use of cholesterol-lowering drug use is associated with lower chance of developing AD. Also, cholesterol seems to modulate the synthesis of Amyloid, as well as control the interaction between Abeta and neuronal membranes that plays a pivotal role in neurodegeneration process (26). Clinical trial is on its way. Thankfully, cholesterol-lowering drugs such as Statin has not much significant side effects, making it easier for researchers to produce large database(25).

Chelation of Zn^{2+} and Cu^{2+} :

Abeta aggregation requires two types of metal ions: Zn2+ and Cu2+(36). Eliminating these two ions by chelation may prevent Abeta deposition. In APP transgenic mice, antibiotic clioquinol could stop the accumulation of Abeta. Further clinical trial is ongoing (25).

Metabolic correction related to insulin deficiency:

Lots of neurodegenerative disease have one aspect in common: energy deficiency. Problems with insulin level is a notable trait for AD (25). Researchers found a correlation between IDE and Abeta, and how brain increasingly lose its ability to utilize glucose (34). Correcting energy metabolism and insulin level in neuronal cells is pharmaceutical companies' new target for AD treatment, despite its uncertainty for success (25).

VI. Conclusion

Statistical pattern of AD seems to be strong enough to indicate the correlation among the eating habit, cholesterol rates, and educational factors with AD. Since there is no pharmaceutical cure developed yet for AD, it would be people's best interest to keep low-cholesterol, healthy diet. Considering the fact that South Koreans are adapting Westernized diet and other westernized risk factors, projected number might be an underestimation. For dietary control has demonstrated its effectiveness, although how it does so is poorly understood, educating the public about the preventative measures is imperative on a governmental level. Special attention is needed for postmenopausal females; hormone balance and cholesterol rate should be monitored regularly, and healthful diet low in saturated fat is recommended. Further experiments are needed to support the idea that soybean consumption is related to the low cholesterol rate, leading to less likelihood of AD. Along with the preventative methods, treatments to reverse the progress of AD needs advancement. Pharmaceutical giants taking their hands off from AD research should reconsider their thoughts once again; although the investment might seem costly, there are still lots of undeveloped strategies to attack the disease. Benefit would surely outweigh the cost, when enormous demand is expected within the next few decades.

Reference

[1] Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, et al. The lifetime risk of stroke: Estimates from the Framingham Study. Stroke 2006;37(2):345–50.

[2] K.A. Matthews et al. Are Changes in Cardiovascular Disease Risk Factors in Midlife Women due to Chronological Aging or to the Menopausal Transition? J Am Coll Cardiol. 2009 Dec 15; 54 (25): 2366-2373

[3] Seung-Ah Go, R.N., Jiyoung Yun, M.D., Jee H. Jeong, M.D. Gender Differences in Risk Factor Prevalence and Cognitive Functions in Alzheimer's Disease; Experience of Ewha Dementia Clinic. Dementia and Neurocognitive Disorders 2007; 6: 34-7

[4] Osuntokun BO, Ogunniyi AO, Lekwauwa GU, Oyediran AB. Epidemiology of age-related dementias in the Third World and aetiological clues of Alzheimer's disease. Tropical and Geographical Medicine. 1991;43:345–351.

[5] Osuntokun BO, Hendrie HC, Ogunniyi AO, Hall KS, Lekwauwa UG, Brittain HM. Cross-cultural studies in Alzheimer's disease. Ethnicity and Disease.1992;2:352–357.

[6] Hendrie HC, Ogunniyi A, Hall KS, Baiyewu O, Unverzagt FW, Gureje O, et al. Incidence of dementia and Alzheimer's disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. Journal of the American Medical Association. 2001;285:739–747.

[7] Yeo G, Gallagher-Thompson D, Lieberman M. Variations in dementia characteristics by ethnic category. In: Yeo G, Gallagher-Thompson D, editors. Ethnicity and the dementias. Washington, DC: Taylor and Francis; 1996. pp. 21–30.

[8] Yamada M, Sasaki H, Mimori Y, Kasagi F, Sudoh S, Ikeda J, et al. Prevalence and risks of dementia in the Japanese population: RERF's adult health study Hiroshima subjects. Journal of the American Geriatrics Society.1999;47:189–195.

[9] http://www.alzheimer-europe.org/Research/European-Collaboration-on-Dementia/Prevalence-of-dementia/Prevalence-of-dementia-in-Europe

[10] McCracken CF, Boneham MA, Copeland JR, Williams KE, Wilson K, Scott A, et al. Prevalence of dementia and depression among elderly people in black and ethnic minorities. British Journal of Psychiatry. 1997;171:269–273.

[11] Critical Perspectives on Racial and Ethnic Differences in Health in Late Life.

[12] Jorm AF. The epidemiology of Alzheimer's disease and related disorders. London and New York: Chapman and Hall; 1990.

[13] http://www.alz.org/downloads/facts_figures_2012.pdf

[14] Bäckman L, Jones S, Berger AK, Laukka EJ, Small BJ. Multiple Cognitive Deficits During the Transition to Alzheimer's Disease. J Intern Med. 2004; 256(3):195–204. doi:10.1111/j.1365-2796.2004.01386.x. PMID 15324363.

[15] http://www.alz.org/national/documents/checklist_10signs.pdf

[16] http://www.alz.org/documents_custom/diagnostic_recommendations_alz_preclinical.pdf

[17] Gurland BJ, Wilder DE, Lantigua R, Stern Y, Chen J, Killeffer EH, et al. Rates of dementia in three ethnoracial groups. International Journal of Geriatric Psychiatry 1999;14(6):481–93.

[18] R. A. Sperling et al. Alzheimer's & Dementia (2011) 1-13, Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimer's Association (2011)

[19] Förstl H, Kurz A. Clinical Features of Alzheimer's Disease.European Archives of Psychiatry and Clinical Neuroscience. 1999;249(6):288–

290.
[20] Gold DP, Reis MF, Markiewicz D, Andres D. When Home Caregiving Ends: A Longitudinal Study of Outcomes for Caregivers of Relatives with Dementia. J Am Geriatr Soc. 1995;43(1):10–6. PMID 7806732.
[21] Weight Loss in the Dementia Patient, Dementia Education & Training Program (2012)
[22] (URL)http://www.alzbrain.org/pdf/handouts/2023.%20%20WEIGHT%20LOSS%20IN%20THE%20DEMENTIA%20PATIENT.pdf
[23] Esler, W.P. & Wolfe, M.S., A portrait of Alzheimer's secretases—new features and familiar faces. Science 293, 1449-1454. (2001)
[24] Craft, Suzanne. Insulin Resistance Syndrome and Alzheimer Disease: Pathophysiologic Mechanisms and Therapeutic Implications.Alzheimer Disease & Associated Disorders: Oct/Dec 2006, vol20, issue 4, 298-301pp.
[25] D.Walsh et al. , Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 416, 535 (2002)
[26] J. Hardy, J. Selko. The Ayloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics. Science 297. (2002)
[27] G. P. Eckert, C. Kirsch, S. Leutz, W.G. Wood, W. E. Muller. Cholesterol modulates amyloid beta-peptide's membrane interactions. Pharmacopsychiatry. 2003 Sep;36 Suppl 2:S136-43.
[28] Lemere CA, Masliah E. Can Alzheimer disease be prevented by amyloid-beta immunotherapy? Nat Rev Neurol. 2010 Feb;6(2):108-19. Review. Erratum in: Nat Rev Neurol. 2010 Apr;6(4):183. Nat Rev Neurol. 2010 Jun;6(6):296.
[29] B.P. Imbimbo, Why did tarenflurbil fail in Alzheimer's disease?Journal of Alzheimer's disease: JAD [2009, 17(4): 757-760] (PMID:19542625)
[30] T. T. Rohn, Proteolytic Cleavage of Apolipoprotein E4 as the Keystone for the Heightened Risk Associated with Alzheimer's Disease, Int. J. Mol. Sci. 2013, 14, 14908-14922; doi: 10.3390/ijms140714908
[31] Alzheimer's Disease Education and Referral (ADEAR) Center,
[32] A Service of the National Institute on Aging (2010)
[33] (URL) http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-medications-fact-sheet
[34] Luo Y, Bolon B, Damore MA, Fitzpatrick D, Liu H, Zhang J, Yan Q, Vassar R, Citron M (October 2003). "BACE1 (beta-secretase) knockout mice do not acquire compensatory gene expression changes or develop neural lesions over time". Neurobiol. Dis. 14 (1): 81–8.
[35] Bogoyevitch MA, Boehm I, Oakley A, Ketterman AJ, Barr RK (March 2004). "Targeting the JNK MAPK cascade for inhibition: basic science and therapeutic potential". Biochim. Biophys. Acta 1697 (1–2): 89–101.doi:10.1016/j.bbapap.2003.11.016. PMID 15023353.
[36] Igbavboa U, Sun GY, Weisman GA, He Y, Wood WG (August 2009). "Amyloid β-Protein Stimulates Trafficking of Cholesterol and Caveolin-1 from the Plasma Membrane to the Golgi Complex in Mouse Primary Astrocytes". Neuroscience 162 (2): 328–38.doi:10.1016/j.neuroscience.2009.04.049. PMC 3083247.PMID 19401218.
[37] L. Xie et al. Alzheimer's beta-amyloid peptides compete for insulin binding to the insulin receptor. J Neurosci. 2002 May 15;22(10):RC221. (2002)
[38] Alzheimer's Disease Facts and Figures, Alzheimer's Association (retrieved in 2013)
[39] V. Tougu et al. Binding of zinc(II) and copper(II) to the full-length Alzheimer's amyloid-beta peptide. J. Neurochem. 2008 Mar;104(5):1249-59. doi: 10.1111/j.1471-4159.2007.05061.x.
[40] Brown P, Jannotta F, Gibbs CJ Jr, Baron H, Guiroy DC, Gajdusek DC, Coexistence of Creutzfeldt-Jakob disease and Alzheimer's disease in the same patient. Neurology. 1990 Feb; 40(2):226-8.
[41] M Preusser et al. Alzheimer-type neuropathology in a 28 year old patient with iatrogenic Creutzfeldt-Jakob disease after dural grafting. Neurol Neurosurg Psychiatry, v. 77(3); Mar 2006.
[42] C.A. Ross, M. A. Poirier. Protein aggregation and neurodegenerative disease. Nat Med.2004 Jul;10 Suppl:S10-7.
[43] L Buée, T Bussiere, V Buée-Scherrer, Tau protein isoforms, phosphorylation and role in neurodegenerative disorders, Brain Research, 2000 -Elsevier
[44] M.C. Irizarry et al., Ab Deposition Is Associated with Neuropil Changes, but not with Overt Neuronal Loss in the Human Amyloid Precursor Protein V717F (PDAPP) Transgenic Mouse. J. Neurosci. 17, 7053. (1997)
[45] Francis PT, Palmer AM, Snape M, Wilcock GK. The Cholinergic Hypothesis of Alzheimer's Disease: a review of progress. Neurol. Neurosurg. Psychiatr. 1999;66(2):137–47.
[46] Alzheimer's Disease Medications Fact Sheet, Alzheimer's Disease Education and Referral Center (retrieved in 2013)
[47] Drug Discovery Opinion, Consultancy for Biotech & Pharma
[48] (URL)http://drugdiscoveryopinion.com/2008/08/novel-mechanism-of-secretase-modulation/
[49] Cooper, Paul. Probing protein aggregation. Highlights in Chemical Biology. Volume-Research News, Aug. 2009. (URL)http://www.rsc.org/Publishing/Journals/cb/Volume/2009/8/probing_protein_aggregation.asp
[50] Crentsil, Victor. The pharmacogenomics of Alzheimer's disease, Ageing Research Review, Volume 3, Issue 2, April 2004, Pages 153–169
[51] R. N. Kalaria et al,. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors, Lancet Neurol. 2008 September; 7 (9): 812-826
[52] Reinli, Kathrin, Block, Gladys.Phytoestrogen content of foods—a compendium of literature values.Nutrition and Cancer.Volume 26,Issue 2, 1996. 123-148