The Risk Factors and Causes for Alzheimer's Disease

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ABSTRACT
Alzheimer's disease, the most common neurodegenerative disease, is categorised by two hallmarks, plaques and tangles, which are formed by accumulated Amyloid-β and hyperphosphorylated tau proteins. However, there is still no treatment or cure for this expensive and lethal disease. Some drugs targeting Aβ and tau proteins theoretically should work, but all fail in the phase 3 trial due to the poor benefits and side effects. This review summarises the epidemiology, genetics, and biochemistry of Alzheimer's disease, showing that age is the main risk factor while the area, income, gender and the surrounding environment can also affect the chances of Alzheimer's disease. In addition, the cause of Alzheimer's disease can be explained by Aβ and tau hypotheses and the genes related to it.

Keywords: *Alzheimer's disease, Epidemiology, Genes, Amyloid, Tau.*

1. INTRODUCTION

Alzheimer's disease is a kind of neurodegenerative disease that is the cause of more than 70% of dementia [1-3]. Now, Alzheimer's disease is becoming one of the scariest diseases in the world. The duration of the disease is around 8 to 10 years. However, its symptoms can last for more than 20 years, bringing massive pain to the patients and increasing the burdens on the whole family [1][2]. Only a few Alzheimer's disease patients have the familial form, usually at a younger age (less than 60 years old), and they inherited the mutated gene from their parents. In comparison, the sporadic form is the usual case which affects mainly older people (over 65 years old) [1-3]. Why and how people get Alzheimer's disease is still not clearly understood. The two most popular hypothesis is the amyloid and tau hypothesis. Amyloid precursor protein (APP) is mis-cleaved by secretases, forming insoluble amyloid-β (Aβ) and then plaques in the brains and vessels [4-6]. The primary genes involved are the APP gene, PSEN1 and PSEN2 gene related to the family of secretases [4][6]. At the same time, Tau proteins are also hyperphosphorylated and aggregated to form tangle, influencing the normal functions of microtubules in the brain [7]. The first Alzheimer's disease case was diagnosed by Alois Alzheimer in 1906. Nowadays, biomarkers are utilised to diagnose the disease instead of the stages of dementia. The biomarkers usually tested the amyloid and hyperphosphorylated tau [1]. Moreover, dementia is the symptom of Alzheimer's disease and other neurodegenerative diseases such as Creutzfeldt-Jakob's disease and Parkinson's disease [1].

This review focuses on the epidemiology, genetics, and biochemistry of Alzheimer's disease, showing the potential risks, two hallmarks of Alzheimer's disease, Aβ and tau, and the genes that leads to them. The author hopes that this review can provide some new thoughts on the risk factors and causes of Alzheimer's disease, thus offering some help to the researchers of Alzheimer's disease and other neurodegenerative diseases.

2. EPIDEMIOLOGY

Scientists have been studying the epidemiology of Alzheimer's disease for over 30 years. The prevalence and the incidence of Alzheimer's disease are still hard to tell. There are two reasons. The most obvious symptom of Alzheimer's disease is dementia, but it is not the only disease that can lead to dementia. According to the research, around 70% of dementia is caused by Alzheimer's disease. Moreover, some other diseases, mainly cerebrovascular disease, can co-exist with Alzheimer's disease. Patients under this situation can be excluded from Alzheimer's disease cases. The technologies are developing fast. Recently, Alzheimer's disease can be detected by imaging and screening the two triggers, amyloid-β peptides and tau in the cerebrospinal fluid in living patients, which have already been approved to be much more effective and accurate than post-mortem methods [1][8].

2.1 Age

The results showed that more than 50 million people worldwide suffered from Alzheimer's disease in 2018, which is double the number of 2009. This number was estimated to triple in 2050, with most patients being older people (more than 65 years old) [3].

The increasing number is mainly due to the worldwide population ageing. Age is the most significant influencing factor in Alzheimer's disease. People can barely have the disease before the age of 60 years. Increasing age can harm neurons and other parts of the brain related to Alzheimer's disease. As people get old, their bodies may not work like teenagers or young adults. Atrophy, vascular sclerosis and blockage, inflammation and many other decreased physical functions resulting from the increasing age lead to a higher risk of Alzheimer's disease. However, a high possibility does not mean everything. Many people are over 90 years old without any cognitive impairment or dementia.

2.2 Area

The prevalence and incidence of Alzheimer's disease are also influenced by the patients' areas (or race). The overall prevalence of Alzheimer's disease was estimated to be 4% in older people worldwide in the 2000s. Regionally, the prevalence is 1.2% in Africa, 2.7% in West Pacific (China), 2.9% in Latin America, 4.8% in Europe, and 6% in the US and Canada [3]. There are around 5 million new Alzheimer's disease patients every year, and the prevalence doubles every five years for people over 65. Around one-twentieth of older people in Europe show dementia, no matter how severe the dementia is. The proportion becomes one third for people aged more than 85. In general, people in West Europe and North America are exposed to a higher risk of Alzheimer's disease.

2.3 Income

Moreover, research demonstrated that the epidemiology of Alzheimer's disease is also associated with income. The overall prevalence in the developing countries is 3.4%, which is much lower than the prevalence worldwide and in the developed countries [3]. In rural areas of India and Latin America, the prevalence (1.5%) was reported to be much lower than in the major cities, such as Havana (6.0%) and São Paulo (5%), which is similar to the rates in Europe and North America [3].

2.4 Gender

The risk is also associated with gender. In 2018, the female Alzheimer's disease patients were two times more than males. Women's lifetime risk is around 20%, while men only have 10%. This is more obvious after the age of 80. Some suggested that it is because the mechanisms of inflammatory and hormone production, especially oestrogen, differ among different genders. Oestrogen regulates the homeostasis of cholinergic neurons, which is vital in sporadic Alzheimer's diseases [9][10]. It is also believed that women have more chances of accumulating tau proteins.

2.5 Physical and mental health

Substantial evidence showed that smoking, obesity, alcohol consumption, high blood pressure and impaired mental health increase the risk of dementia and Alzheimer's disease [11]. The basic intervention, especially for mid-aged people, is maintaining healthy blood pressure, controlling body weight and blood glucose level, and living an active life. However, even though many people exercise every day, a lot of them still do not understand the importance of having good vascular health. Education about it in school and college is necessary for their mid-age and elder life.

3. GENETICS

3.1 The familial form of AD

Genetically, Alzheimer's disease has two types: sporadic and familial forms. Familial Alzheimer's disease only accounts for less than 10% of all cases. Most familial Alzheimer's patients are also termed early-onset Alzheimer's patients because they are diagnosed in their 40-50s. It is found that familial Alzheimer's disease is more common in people with Down syndrome. Familial Alzheimer's disease patients are more likely to develop brain abnormalities. Familial Alzheimer's disease is caused by the mutation of the following three genes, amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2), and they are all autosomal dominant [1][4]. The disorder of any of them is sufficient to cause familial Alzheimer's disease.

The APP gene is found on the long arm of chromosome 21 in humans, and it contains at least 18 exons. Several forms of APP with different numbers of amino acids can be produced from the APP gene due to alternative splicing. The most seen form in the central nervous system is APP 695. APP proteins are cleaved into peptides and then produce Aβ, which is considered the main component of plaques. Aβ also varies due to different lengths (38-43 amino acids). Isoform Aβ42 is more likely to aggregate and form toxic plaques [12][13]. Aβ is a regular metabolic product in the nervous system, and the half-life of Aβ in healthy people is around 9 hours, which is faster than the rate of production. If the APP gene is mutated, the steady statue will be broken, more and more Aβ is produced and the percentage of Aβ42 increases. Evidence showed that APP knockout in mice is not lethal, but it can seriously reduce the body and brain weight. The mice are unlikely to move, and

many of them suffered from gliosis, agenesis and seizures. Besides, APP also controls the calcium channel handling in some GABAergic neurons [6]. Moreover, PSEN1 and PSEN2 are homologous genes found in most familial Alzheimer's diseases. PSEN1 is found on chromosome 14, while PSEN2 is on chromosome 1. These two genes are associated with βAPP processing and Notch signalling. They encode part of one enzyme that cleavages APP protein γ-secretase. Mutations of these two genes can also lead to an increase in Aβ production, especially Aβ42. Mutated APP, PSEN1 and PSEN2 dramatically raise the risk of early-onset Alzheimer's disease [1][6][14-16]. Luckily, evidence showed the rate of sporadic Alzheimer's disease is not affected by these three genes.

3.2 The sporadic form of AD

The other form is considered sporadic Alzheimer's disease. Both genetics and the environment play an essential role in this form. The only gene confirmed to increase the risk of Alzheimer's disease is APOE (Apolipoprotein E) [1]. Even though APOE mutation is only found in 30-60% of cases, it is still the main gene risk of sporadic Alzheimer's disease. APOE can be found on chromosome 19 in humans, and it has three forms: epsilon 2, 3, and 4. APOE2 decreases the risk while the mutation of APOE4 dramatically increases the risk, whether homozygous or heterozygous. APOE regulates the homeostasis of cholesterol, which seems to have nothing to do with Alzheimer's disease, so it is still unclear how the mutation of only one APOE4 allele can increase the risk by three times. Some hypotheses indicated that APOE4 mutation leads to the imbalance of lipids and cholesterols in the nervous system, which affects Aβ metabolism [2][13][14]. Besides the APOE gene, there are still loads of genes identified Genome-Wide Association Studies such as BIN1, ABCA7, and CD33 found in all races, and CLU, CR1, and PICALM mainly recognised in Caucasians.

The genes above mainly increase the risk of Alzheimer's disease by influencing the normal activity of Aβ, which results in plaques. Another hallmark for Alzheimer's disease is the tangle. MAPT (Microtubule Association Protein Tau) gene on chromosome 17 is responsible for Tau protein production, and a mutation of the MAPT gene leads to the production of hyperphosphorylated Tau instead of the normal ones. The hyperphosphorylated tau proteins are toxic and can no longer regulate neuronal polarity and signalling. Synaptic degeneration is also identified due to MAPT mutations. In the brain of Alzheimer's disease patients, hyperphosphorylated Tau is located at the same place as TDP-43 proteins, encoded by the TARDBP gene [16]. Mutations of TARDBP and TDP-43 are detected in many other neurodegenerative diseases such as Parkinson's disease.

Identification of the genes that lead to Alzheimer's disease does not mean we fully understand its pathogenesis. Sometimes, the explanations of how a gene mutation can lead to Alzheimer's disease can conflict with each other. That is why the environment where people live is so important. Gene is not everything. Having APOE4 does not mean 100 % sporadic Alzheimer's disease. The interactions between the genes and the environment matter [17][18]. When a person is exposed to tobacco, alcohol, pesticide and air pollution, the risk is higher.

4. BIOCHEMISTRY

Unfortunately, the biochemistry of Alzheimer's disease is not fully understood. The only few visible things under the microscopy show the amyloid plaques and the neurofibrillary tangles in the brain of Alzheimer's disease. Plaques are mainly insoluble APP protein deposits around the neurons, while tangles are fibres inside the neurons produced by Tau protein. Since the research on Alzheimer's disease keeps going deep, there are different hypothesises on how the disease is caused. The oldest one is the cholinergic hypothesis. Besides, the inflammatory and isoprenoid hypotheses are also proposed as explanations. However, the two hypothesises believed by most people are still the amyloid and tau hypothesis.

4.1 The amyloid hypothesis

The amyloid hypothesis was first raised in 1992 due to the observation of amyloid plaques formed by aggregated Aβ [19]. The cleavage process or the APP processing is associated with three enzymes, α, β, and γ-secretase [4-7][14][19] (Figure.1).

Complete APP proteins are first cleaved by α-secretase or β-secretase. The products are cleaved again by γ-secretase. There are two pathways to process APP proteins distinguished by the enzymes found in the first part of the processing. The first one is the non-amyloidogenic pathway, which is how most APP proteins are cleaved when healthy. The full-length APP proteins are cut by α-secretase. The toxic amyloidogenic pathway where β-secretase could be found also happens in normal situations, but much more in Alzheimer's patients. When the APP protein is located on the cell surface, it is transmembrane. It has a long N-terminal ectodomain, a short C-terminal domain which is part inside the cell, part inside the cell membrane, and a whole Aβ domain in the middle which has 37-43 amino acids.

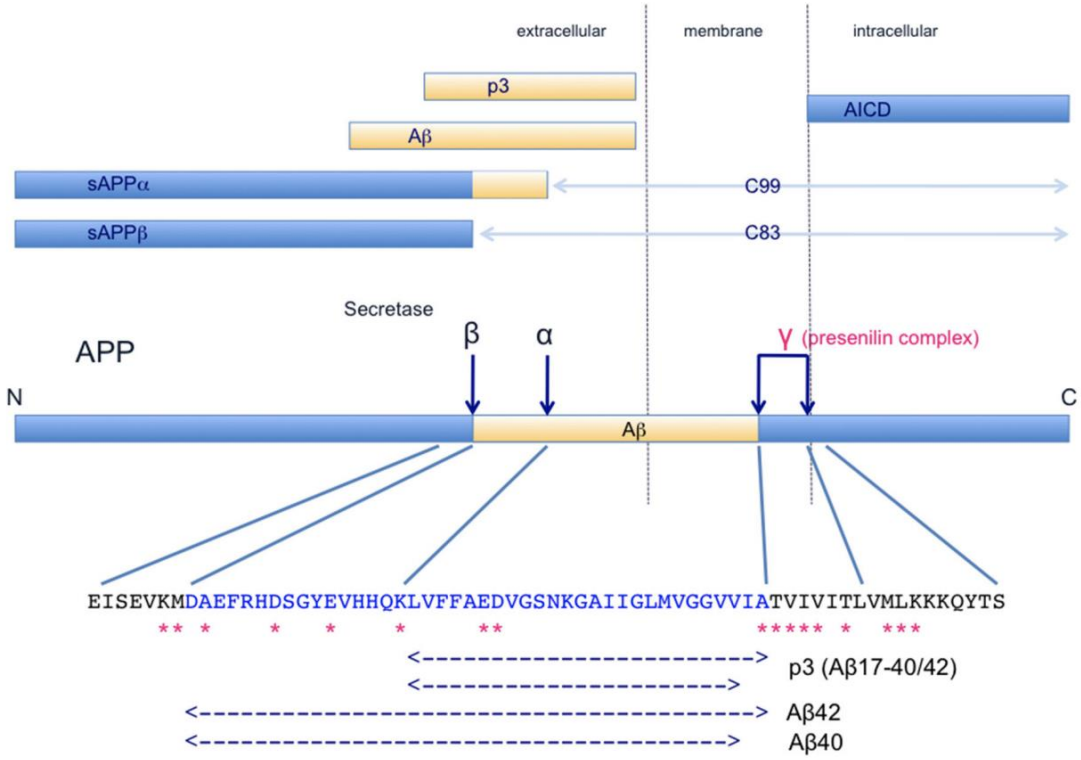

Figure 1 The schematic of APP processing. APP proteins can be cleaved by β-, α-, and γ-secretase [7].

In the nonamyloidogenic pathway, the APP is cleaved by the α-secretase, and the cut site is located within the Aβ, at the bond between the 16th and 17th amino acid (Lys16 and Leu17). The protein is then divided into two parts, sAPPα and α-CTF (α- C-terminal fragment). In contrast, the cut site is different in the amyloidogenic pathway. BACE1, the common type of β-secretase cuts the Aβ mostly on Asp1 and sometimes Glu11 results to an sAPPβ domain and β-CTF. The next step for both pathways is the γ-processing. The α-CTF and β-CTF are cut again by γ-secretase. P83 and Aβ are produced respectively. The sites for γ-processing also vary just like β-processing. The enzymes cut on usually the 40th and sometimes 42nd, which leads to the different Aβ, Aβ40 and Aβ42 in the amyloidogenic pathway. Aβ42 is shown to be more toxic to the nervous system. Both Aβ40 and Aβ42 are found in the cerebrovascular plaques, and only Aβ42 is not enough for the onset of Alzheimer's disease. However, how Aβ combines and aggregates to each other and triggers the disease is still unclear. Recently, more cut sites have been identified, such as Aβ46 and Aβ49 (ξ and ε sites). Aβ can oxidase cultured neurons and trigger apoptosis in vitro. The overexpression of the APP gene leads to more aggregated Aβ and neuronal injuries. As people are getting old, the ratio of Aβ42/Aβ40 in the CSF decreases while it rises in the brain, meaning that less Aβ is transported out of the brain, and the genes encoding α-secretase are more likely to be acetylated, which decreases the chance of nonamyloidogenic APP processing. The whole hypothesis is reasonable and accepted by many people even though it is not fully established. Because of this, the mechanism inside the theory becomes a potential target to treat Alzheimer's disease. The drugs in the trial include Bapinezumab, Solamezumab, Crenezumab and Aducanumab that targeted directly at Aβ, Semagacestat and Tarenflurbil as γ-secretase inhibitor or modulator, and CNP52p, Lanabecestat and Atabecestat as BACE1 inhibitor [20]. Theoretically, these drugs should work, but they did not. Most drugs did not improve cognition. Patients did not perform better on cognitive tests, even though the level of Aβ decreased. Sometimes, the drugs even resulted in serious side effects such as Semagacestat, which increased the risk of skin cancer. More drugs could not even pass the animal test. The blood-brain barrier is also a problem, meaning that the drug should always be small molecules.

4.2 The tau hypothesis

The tau hypothesis is also well believed. Tau is a kind of protein located at the axons of neurons. It contributes to the production of the microtubule, which forms tubulin and keeps the stability of tubulin [7][16]. Tau has six isoforms in the adult human brain with different mRNA splicing. The 3-repeat tau and 4-repeat tau are included in the hypothesis. The insertion of exon 10 is the only difference between these two tau proteins (Figure. 2).

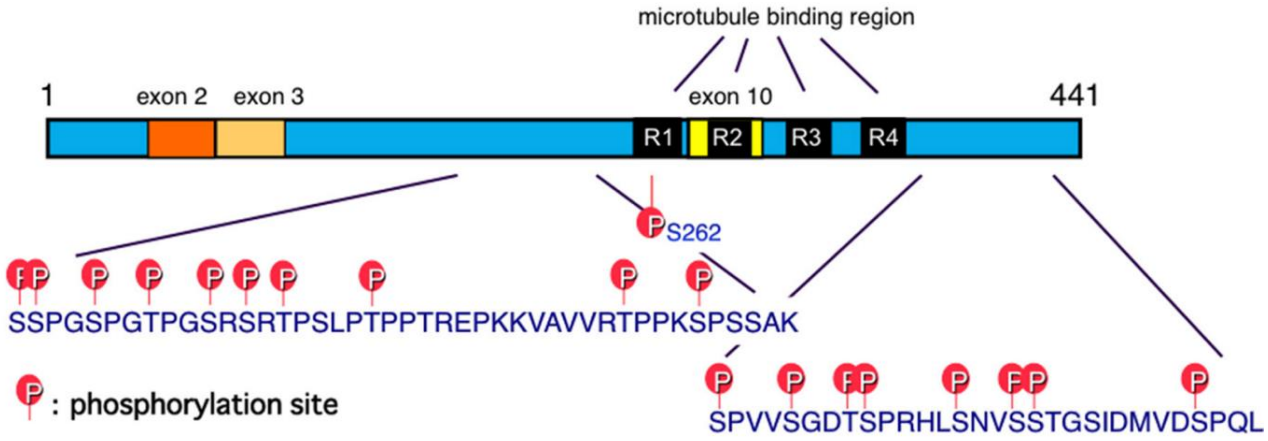

Figure 2 The schematic of tau. Only 4-repeat tau are produced with exon 10. The phosphorylation sites are also shown [7].

Usually, the 3R and 4R tau can only be found in the axons of human neurons. However, in the brains of Alzheimer's disease patients, they are hyperphosphorylated and accumulated, forming neurofibrillary tangles in the cell bodies of neurons and threads in the dendrites or axons [7] [21]. The mutation, mislocalisation and hyperphosphorylation reduce the chance of tau protein to bind with microtubules, so they would not be able to regulate tubulins. Furthermore, the hyperphosphorylated tau proteins are much more stable than the normal ones, which means they are barely degenerated or broken down, causing damage to the transport and signalling of the neurons. Braak's stage can be the evidence of this hypothesis [22]. The whole neurofibrillary changes can be divided into six stages, according to the patterns and locations of the lesion (Figure.3).

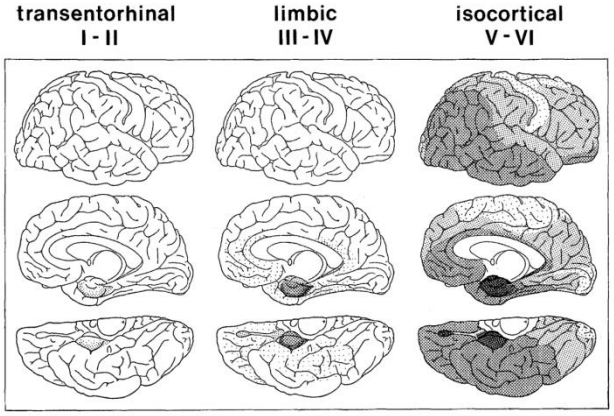

Figure 3 The changes of tangles and threads in the brain at different stages of Alzheimer's disease [22].

Stage I-II is called the transentorhinal stage. Mild tangles and threads are affecting the transentorhinal region. In the limbic stage (Stage III-IV), the situation worsens. The entorhinal region is also affected, while the last two stages (the isocortical stage) exhibit a severely affected isocortex and surrounding areas by tangles and threads, and the density of tangles is also increasing. Besides, many other neurodegenerative diseases related to chromosome 17 show tau abnormalities, including frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) [7]. Several types of tau genes were identified in the patients, proving that tau protein triggers neurodegenerative and even Alzheimer's disease.

5. CONCLUSION

Alzheimer's disease has been studied for more than 20 years. However, there is still no treatment for it. It is time to review the epidemiology, genetic risks and biochemistry of Alzheimer's disease. This review shows some risk factors of Alzheimer's disease such as age, area, income, and gender, and also Aβ and tau hypotheses that explain the cause of Alzheimer's disease and the genes related to it. Future research can focus on studying a new path such as targeting the metabolism of APP instead of still focusing on the production of Aβ and hyperphosphorylated tau.

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