

A General Understanding in Alzheimer's Disease

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Abstract. Alzheimer's Disease (AD) normally happens in people with age of 65 or above, and it is the most common cause of dementia. It suggests that the total cost of dementia worldwide will reach US \$2 trillion by 2030 or even more, due to more people being aware of it these years and having the ability to take a diagnosis and treatment. This review about AD is mainly focused on neuropathology, symptoms, risk factors, current treatments including traditional pharmacological therapies and newly developed disease modifying therapies (DMTs) of AD. Although the cause of AD has not been fully discovered, it is sure that AD is proved with pathology of the accumulation of 2 aggregates appearing in the brain, which are extracellular A β plaques and intracellular neurofibrillary tau-containing tangles. DMTs are known to be treatments that have an effect on the pathology of AD. Currently the two approved DMTs (Aducanumab and Lecanemab) are both A β -directed monoclonal antibodies, but there are tau-directed therapy trials going on. Although DMTs are only used at an early stage of AD progression and have been only approved very recently, they have less side effects and have more benefits compared with traditional drugs used to relieve decline in cognitive symptoms without altering the pathology of AD.

Keywords: Neuropathology, symptoms, risk factors, treatment.

1. Introduction

Alzheimer's Disease (AD) was first discovered by Alois Alzheimer, a clinical neuroanatomist and psychiatrist who reported an article named "A peculiar severe disease process of the cerebral cortex" on November 3, 1906. As a common worldwide age-associated disease, quality of life is significantly decreased in severe AD patients and their caregivers due to the symptoms like cognitive impairments, memory loss, worsening in language, executive dysfunction and even change in personality. Neuropsychological testing and clinical interview are usually used to observe moderate to severe cognitive impairments of potential AD patients during the diagnosis. What's more, the two proven biomarkers associated with AD, beta-amyloid plaques and tau tangles, can be detected and measured by amyloid-PET and tau-PET scanning in diagnosis. Also, unfortunately, AD patients ultimately die in 3-9 years on average after being diagnosed [1, 2]. This review will mainly focus on neuropathology, symptoms, risk factors, current treatments of the AD.

2. Neuropathology

AD is known to be associated with extracellular senile plaques of aggregated beta-amyloid (A β) peptides and intracellular hyperphosphorylated tau protein rich intraneuronal neurofibrillary tangles (NFTs). The two aggregates can lead to loss of synapses, loss of neuron functions and cause apoptosis of neurons as well as inflammatory responses in the brain to occur [1].

2.1. A β Plaques

Beta-amyloid plaques are insoluble toxic accumulations of fallen pieces (A β monomers) from amyloid precursor protein (APP) that clump together in the synapses of AD patients. The human amyloid precursor protein is a single-pass integral membrane protein found in many cell types but mainly in synaptic terminals of neurons [1, 3, 4].

In AD patients, mutated APP is cleaved by β -secretase and γ -secretase into several amino acid pieces, 43, 45, 46, 48, 49 and 51 amino acids and form A β 40 and A β 42 monomers. This process either happens directly on the cell surface membrane, where A β peptides are released into synapses straight

away, or happens in endosomes, where APP is re-internalised, and then A β peptides are transported into extracellular space or being digested by lysosomes. Large and insoluble fibrillar A β monomers can form plaques, and soluble oligomeric A β monomers can flood inside the brain and gradually form larger soluble neurotoxic A β oligomers and aggregates into insoluble A β plaques. The process is shown as figure 1. Increase in A β 42/A β 40 ratio can promote the production of A β fibril, which leads to neurotoxicity and accelerates tau pathology. A β plaques can cause the loss of synapses, stimulation of astrocytes and microglia, damage to axons, alteration of dendrite spines, synaptic plasticity and therefore cognitive impairments [1, 2, 5].

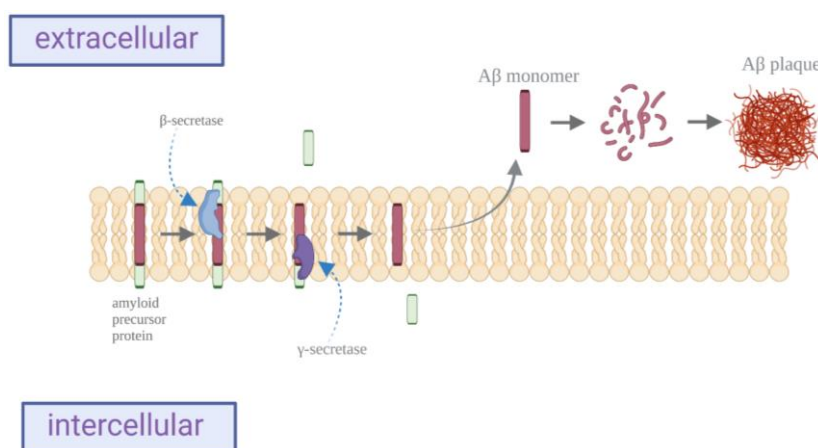


Figure 1. Direct formation of extracellular A β plaque (Created with BioRender.com)

2.2. Tau Tangles

Tau-containing NFTs are insoluble twisted fibres inside neurons and are formed from tau proteins. Tau is a structural protein contained in microtubules that helps stabilise the microtubules by undergoing tau dephosphorylation activated by phosphatase. Those microtubules have a role of transporting nutrients and other substances inside nerve cells. However, research shows that the amount of phosphatase is relatively low in AD patients' brains compared with normal functioning brains. Therefore, instead of tau dephosphorylation, tau proteins undergo hyperphosphorylation and misfolding. This makes tau proteins detach the microtubules, which leads to the breakdown of microtubules. As those microtubules are damaged, the communication of substances and nutrients are disrupted inside a neuron [1, 3].

Hyperphosphorylated tau proteins are also more easily clumped together and this can lead to the formation of tau-containing NFTs, shown as figure 2. Moreover, in some stages, NFTs can be twisted and form paired helical filament (PHF), which leads to the loss of cytoskeletal microtubules and tubulin-associated proteins. Together, the disappearance of microtubules and formation of tau tangles lead to the loss of neuronal functions and gradually cause apoptosis of nerve cells to occur [1, 2, 5].

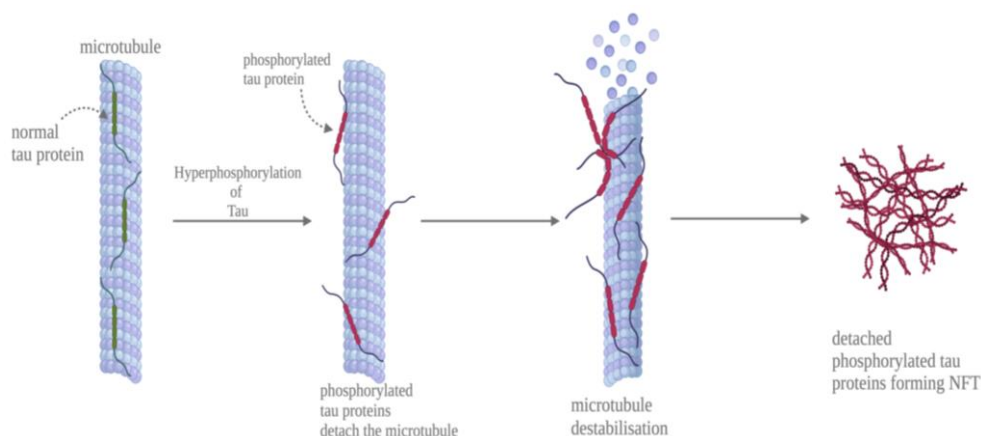


Figure 2. Formation of NFT (Created with BioRender.com)

3. Symptoms

Also, as mentioned, the formation of the two aggregates can lead to the synaptic damage and loss of synapses, preventing neurotransmitters from binding to the receptors and therefore cause symptoms like cognitive impairments. Cognitive impairment refers to people having trouble in memorising (cannot remember things or false memory), learning new things, concentrating in their work or making decisions in their daily life. Severe cognitive impairment can also result in people disable to live independently [6].

Mild to moderate AD starts with an increase of confusion, worsening in language and eventually memory loss, which short term memory loss is more common compared to the loss of long term memory. Many AD patients are found that they cannot recall things they did recently, but can clearly state their experience in childhood. In the advanced stage, AD patients can lose their ability to live independently and to communicate with other people. Moreover, apoptosis of nerve cells happens in patients with severe AD symptoms, leading to a decrease in the brain volume and ultimately to the death of AD patients.

Other symptoms like change in personality and behaviour can also happen in AD patients.

4. Risk Factors

AD is associated with various risk factors, including genetics, age, biological gender, heart disease, high blood pressure, environmental factors and type 2 diabetes, etc.

4.1. Genetics

First of all, family history and genetics is one of the most important ones. Heredity of risk genes can increase the risk of developing AD and heredity of the deterministic gene can directly cause AD. Worth to be mentioned, 70% of AD patients have relevant genetic factors such as inheritance of an autosomal pattern or have mutations in dominant genes responsible for AD-linked proteins [1, 5].

The main mutation factor is the mutation in APP gene located on chromosome 21, which lead to APP being cleaved by β and γ secretase and produce $A\beta$ monomers that result in the accumulation of $A\beta$ plaques. There are 30 identified mutations in the APP gene and 25 of them are associated with the mechanism of AD, which happens around the secretase cleavage site and can cause an increase in $A\beta_{42}/A\beta_{40}$ ratio. As mentioned, increase in $A\beta_{42}/A\beta_{40}$ ratio results in accumulation of $A\beta$ fibril, which causes neurotoxicity and promotes tau pathology. The formation of NFTs leads to nerve cell death and neurodegeneration. Also, the E693 Delta mutation promotes the synaptotoxic $A\beta$ formation [5].

Presenilin-1 (PSEN-1) and presenilin-2 (PSEN-2) are also two autosomal dominant genes associated with Early-onset Alzheimer's Disease (EOAD), located respectively on chromosome 14 and chromosome 1. Early-onset AD is when AD happens to people who are under 65 years of age, which takes up a very small percentage of AD patients and usually happens in their 40s and 50s. PSEN-1 protein is associated with the activation of γ -secretase binding to its substrate, which is involved in part of the $A\beta$ monomer formation. Loss in synaptic functions and memory impairment of mice are shown in knockout studies of PSEN-1. PSEN-1 mutations, which are mainly substitutions of one or two amino acids, can cause a decrease in $A\beta_{40}$ level, so the $A\beta_{42}/A\beta_{40}$ ratio is increased. PSEN-2 mutations are rarer than PSEN-1 mutations, but also associated with increasing γ -secretase activity as well as a change in $A\beta_{42}/A\beta_{40}$ ratio [5].

Other mutations in neuron-related genes such as ApoE, ABCA1, CLU, BIN1, ECSIT, ESR can also increase the risk of developing AD.

4.2. Other Risk Factors

Age is another important risk factor of AD. After reaching 65 years old, the risk of developing AD doubles every year and increases to one third after the age of 85. However, age does not cause AD directly. Heart disease, high blood pressure, high cholesterol level, diabetes and stroke which are all

associated with increasing age, are responsible for AD. Because brain functions are highly dependent on blood supplies, problems of any part in the brain-heart connection have a chance to cause the mechanism of AD to take place. Furthermore, increase in age or high blood glucose level can lead to the increase and acceleration of tau phosphorylation degree.

It also suggests that AD is sex-linked. Females take up about two thirds of the AD patients, but also survive a longer time after the diagnosis compared with male patients. The difference between sex in developing AD can rise up from the life-style differences, sex chromosomes, sex hormones, brain structures and so on [7].

Head injury and environmental effects such as heavy or trace metals, air pollution, infections and diet are also linked with AD. For diet, the intake of high glucose and cholesterol level food can increase the risk or cause cardiovascular disease (CVD), and CVD is associated with increasing the risk of AD. Therefore, those foods can result in increasing risk of developing AD. Type 2 diabetes (T2D) is also shown as a risk factor of late-onset AD, which is highly associated with diet as well. What's more, studies have shown that vitamins, fish and antioxidants have an effect on decreasing the risk of AD [1, 5].

5. Current Pharmacological Treatments

Currently there are no drugs that can cure AD but only two classes of drugs approved by FDA for slowing the AD progression or temporarily relieving the symptoms, including cholinesterase inhibitors (ChEIs) such as Galantamine, Rivastigmine and Donepezil for mild to moderate AD treatments. And partial N-methyl-D-aspartate(NMDA) antagonist Memantine for moderate to severe AD treatments. None of them can affect AD pathology [5].

5.1. Cholinesterase Inhibitors (ChEIs)

ChEIs are chemicals that bind with cholinesterase enzymes (acetylcholinesterase, AChE and butyrylcholinesterase, BChE) to prevent them from breaking down the neurotransmitters acetylcholine(ACh) and butyrylcholine(BCh). Medicals of AD treatment are AChEIs which block AChEs to increase the level of AChs in the synapses, because lacking ACh is highly associated with cognitive symptoms of CNS. ACh is an important neurotransmitter at neuromuscular junction and also a neuromodulator in cholinergic neurons. As a neuromodulator, it is responsible for cognitive functions such as memory, especially in the hippocampus-dependent learning. Research shows that in AD patients, there is a decrease in cholinergic neurons and the levels of choline acetyltransferase (ChAT), which is an enzyme involved in synthesis of acetylcholine(ACh). Therefore, ChEIs can help relieve the cognitive deficits caused by the reducing level of ACh in AD patients through binding with AChE. Some statistical data does show that BChE is associated with increasing activity of AChE in AD patients, which suggests that moderate to severe dementia may be associated with abnormal BChE level [5, 8].

Speaking of specific drugs, the three (Galantamine, Donepezil and Rivastigmine) approved by FDA can be separated into 2 classes, and all of them are used on AD patients with mild to moderate symptoms. Rivastigmine is a pseudo-irreversible ChEI, which has an immediate effect of blocking AChE for up to 10 hours and BChE for 3.5 hours. It is associated with decreases in both AChE and BChE. Donepezil and Galantamine, which are rapidly reversible ChEIs, have an effect on increasing the level of AChs in the Cerebrospinal fluid (CSF). Galantamine helps increase the level of AChs in two ways. Firstly, it can act as an AChE competitive inhibitor, which is the same with Donepezil. Secondly, it can bind with the α -subunit of nicotinic ACh receptors to activate it [5, 9].

Side effects are highly dependent on doses, including nausea, vomiting, salivation, anorexia, etc. Some patients also showed a decrease in heart rate when taking the medicines. What's more, Rivastigmine can lead to skin irritation, redness or rash [10].

Furthermore, although ChEIs is the current main pharmacotherapy treating AD (mainly at an early stage and for short term uses), there is still controversy about it. Most of the studies show that there

is no significant evidence that ChEIs can result in an increase of phosphorylated tau formation or have an effect on A β pathology. However, a study in the UK does show that compared with untreated AD patients, for those who are receiving ChEIs, there is an increase in the amount of phosphorylated tau in the cerebral cortex but no significant decrease in A β plaques. Therefore, there are still possibilities that ChEIs can promote tau pathology and accelerate the progression of AD. This also provides an explanation of why ChEIs become unhelpful when used as a long-term therapy [2, 11].

However, there are still several limitations of ChEIs. One of them is the usage of ChEIs also means the continuous production of ACh and the activation of its receptor. So eventually patients can develop tolerance to the drug. Moreover, because rivastigmine is not an AChE selective drug, although the decrease in BChE can have individually dependent advantages on AD patients, it can also interrupt non-neural functions and are associated with toxicities. Galantamine and donepezil also show toxicity during short term trials. Due to the toxicity of the drugs, there are limited doses when giving the drugs to AD patients. This results in safety problems and limited efficacy of ChEIs.

5.2. Partial N-methyl-D-aspartate(NMDA) Receptor Antagonist

NMDA receptor (NMDAR), a glutamate receptor, increases the level of calcium ions influx, which activates signal transduction. This can cause gene transcription to happen on those genes associated with the formation of long-term potentiation (LTP), which plays a role in synaptic plasticity, neurotransmission and memory formation. However, in AD patients, the overreaction of NMDAR interrupt the level of calcium ions and cause overstimulation of glutamate, which is an important neurotransmitter maintains normal brain functions in the CNS and the ability to study and memorise when it is at a correct concentration. The overstimulation of glutamate results in synaptic dysfunction, excitotoxicity, neuron death as well as influencing the cognitive functions [5, 12].

NMDA antagonists, or NMDAR antagonists prevent the excessive action of NMDAR and therefore decrease the influxed calcium ions to make the neuron function normally. Memantine is approved by the FDA for symptoms like memory loss in dementia and the only approved NMDA antagonist for moderate to severe AD, which can be used solely or combined with AChEI Donepezil. Memantine works as a low affinity, non-competitive antagonist that binds selectively to open the channel allowing calcium ions flowing at a right concentration. This lowers the over-activation of NMDAR and the effect of glutamate, which have an effect on relieving some of the cognitive symptoms and neurobehavioral symptoms [13].

Because of the low affinity of Memantine, it is safe and well-tolerated to use without affecting the efficiency of other neurotransmitters. Also, it does not stimulate the neuropathology of any mechanisms in AD or worsen the symptoms compared with ChEIs. However, this also means that it has limited effects on the disease and is usually replaced by glutamate in a short time due to the high concentration of glutamate in brains affected by AD. Studies show that memantine as a monotherapy of AD treatment does improve the loss of cognitive functions in AD patients compared with placebo, but with a low efficacy [5, 13].

No known withdrawals when memantine is used solely according to studies. It is well-tolerated and safe to use, with mild side effects such as dizziness, headache, confusion and somnolence when given to AD patients at the maximum dose twice daily.

5.3. Combined Therapy

As mentioned above, memantine can be used as a combined therapy with the AChEI Donepezil for treating AD patients with moderate-to-severe dementia who have been receiving a constant AChEI (donepezil) therapy. This add-on dual combination therapy works for both short term (6-12 months) and long term (12-36 months) trials to decelerate the worsen of cognitive impairments. The use of memantine also reduces the side effects when using ChEIs only. This combination shows good results in both tolerance and safety. However, there is no significant increase or difference in improving the symptoms compared with AChEI monotherapy or placebos [10, 14].

6. Disease-modifying Therapies (DMTs)

Monoclonal antibodies can be used as a treatment of AD that affects the underlying mechanisms of the disease, but still not a cure. Currently there are several amyloid beta-directed antibodies trials going on but only two of mabs are approved by FDA for AD treatments, which are Aducanumab (approved on June.7.2021) and Lecanemab (approved on July.6.2023). Both of them are immunotherapies for early AD with mild cognitive impairments or mild dementia and targeting on the A β plaques to alter and slow the progression [15].

However, Amyloid-related imaging abnormalities (ARIA) are associated with the removal of A β . Therefore, it suggests that ARIAs happen as a dose-dependent side effect in all of the amyloid-modifying therapies, including Aducanumab and Lecanemab, and especially in Aducanumab therapy. ARIAs are abnormal observations of AD patients' brains detected by MRI scanning. ARIAs happen more easily in patients with the ϵ 4 allele of apolipoprotein E gene (APOE4), one of the strongest risk factors of late-onset AD (AD happens on people who are 65 years old or older) [1].

Aducanumab is the first DMT for AD approved by FDA, which is an anti-A β human immunoglobulin 1 (IgG1) mab that selectively targets aggregated A β , including A β plaques and high molecular weight A β oligomers (ABOs). It binds with A β peptide on a linear epitope formed by amino acids 3-7. This stimulates microglia to cleave A β in the brain and slows the progression of A β formation and helps reduce cognitive decline. The results showed a beneficial effect in both mice studies and clinical trials. It also has a good result in safety and tolerance, apart from ARIAs [15].

Lecanemab is an humanised A β -directed IgG1 mab with high affinity to soluble A β protofibrils, which is neurotoxic and plays an important role in AD pathology. Same as the mechanism of aducanumab, lecanemab alters the AD pathology by cleaving A β in early AD and reducing the decline in cognitive functions. Compared with aducanumab, it has a lower rate of getting ARIAs as a side effect and a better efficacy. Lecanemab is also well tolerated and more safe to use according to both animal and human trials [15, 16].

7. Conclusion

In conclusion, AD is a multifactorial neurodegenerative disease associated with the formation of aggregates of both extracellular A β plaques and intracellular NFTs. Both pathologies can cause loss of synapses, damage in neurons and eventually nerve cell death. Apart from being the cause of most dementia cases, AD can also lead to cognitive impairments, memory loss, change in personalities and other symptoms, and ultimately death. Genetics, family history, age, sex, diabetes, heart diseases and environmental factors are seen as risk factors of AD. EOAD and LOAD are associated with different mutations but genetics is a great risk factor of both types of AD. Regarding safety and efficacy, DMTs are a trend of AD treatments compared with traditional pharmaceutical therapies like ChEIs and NMDA receptor antagonists, which in this case ChEIs are Galantamine, Rivastigmine and Donepezil, NMDA receptor antagonist is Memantine. DMTs work by altering the underlying pathology to slow the progression of AD and improve the cognitive conditions of AD patients, whereas ChEIs and NMDA receptor antagonists are symptomatic treatments that can only help with the relief in cognitive impairments in a short period of time. Although the currently approved DMTs, Aducanumab and Lecanemab, are both targeting soluble A β plaques, immunotherapies targeted on the other pathology tau tangles are already undergoing trials. Worth to be mentioned, psychological care is also seen as an important way to slow the AD progression and is beneficial for AD patients' mental health.

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