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Review of Alzheimer's disease and treatments

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disease that primarily affects older adults and is characterized by progressive memory loss and cognitive dysfunction. The disease is the most common type of dementia worldwide and imposes a significant burden on patients, families and society. More than 50 million people worldwide are affected by Alzheimer's disease, placing enormous financial strain on healthcare systems and families. The main molecular metabolic pathways of Alzheimer's disease include amyloid beta protein metabolic pathway and tau protein phosphorylation pathway. Abnormal accumulation of amyloid beta protein in the brain to form plaques, and excessive phosphorylation of tau protein to form neurofibrillary tangles, these pathological changes lead to nerve cell damage and death, resulting in the gradual loss of cognitive function. Current treatments can only slow the progression of the disease or alleviate symptoms and cannot completely cure AD. Finding effective treatment and intervention strategies can not only significantly improve the quality of life of Alzheimer's patients, but also reduce the burden of the disease on society and families. This article will review the background and epidemiology of Alzheimer's disease, discuss its main molecular metabolic pathways in detail, and review the current status of treatment, with a view to providing references for future research and treatment strategies.

Keywords: Alzheimer's disease, current symptoms and mechanisms, references for treatment.

1. Introduction

Alzheimer's Disease (AD) is a chronic and progressive, neurodegenerative disease which characterized by memory loss, cognitive decline, and behavioral problems, making a hung impact on daily life of patients.

1.1. History of AD

A woman who was born in a working-class family of Kassel, Germany on May 16th, 1850, named Auguste Deter. In 1901, she exhibited uncontrollable behaviors such as delusions and memory loss and was admitted to a psychiatric hospital under the care of Alzheimer's, who became interested in the condition and began carefully documenting and studying it. In 1906, the deceased Auguste's brain was biopsied, and the symptoms and changes found in the biopsy, such as neurofibrillary tangles and atherosclerosis, were reported. Finally, in 1910, the dementia was first named Alzheimer's Disease by the German physician Emil Kraepelin[1] .

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1.2. Clinical features of AD

One of the important symptoms of AD is behavior disorder, AD patients may experience short-term memory loss or repeat the same behavior, and at the same time, they may become disoriented in familiar tasks. Furthermore, speech disorders can also appear in patients, resulting in unclear vocabulary expression and affecting communication skills. Their personality will also change, there will be stubborn impulsive behavior, and even make inappropriate behavior. Finally, with the decline of cognitive function, they will gradually lose interest, become passive, and show a change in emotional state [2]. As for the AD's psychological symptom, commonly, people with AD experience symptoms of depression, persistent feelings of sadness, helplessness, and decreased interest in daily activities, as well as feelings of anxiety, insecurity and fear about the environment and the future. Moreover, in the advanced stages of the disease, some patients may experience hallucinations (as seeing or hearing things that are not there) and delusions (as believing things that are not true). [2] In addition, people have AD can also affect appetite and eating habits, affecting nutritional status. Patients may also experience reduced motor capacity, such as slow movement and uncoordinated limbs, which increases the risk of falls. It can also reduce the patient's judgment; difficulty understanding other people's words and even misunderstand other people's intentions. These symptoms have a significant impact on the quality of life of patients and also pose great challenges for family members [3] .

1.3. Diagnosis of AD

Currently, the diagnosis of AD requires an evaluation of a person's medical history and symptoms, the former including the person's family history, the latter including assessment of memory, judgment, language ability, daily living ability and other indicators. In this stage, doctors often use standardized neuropsychological tests to assess memory attention and other cognitive functions. After that doctors will do the specific medical test such as CT scan or MRI which can be used to rule out other brain diseases that may lead to dementia, such as brain tumors, strokes, or brain atrophy. They can also look for structural changes in the brain, such as hippocampus atrophy. As for the PET scan, it can be used to detect the protein aggregation in the brain to check for symptoms. In addition, there are also biochemical tests such as cerebrospinal fluid analysis to check for levels of amyloid beta and tau proteins, which are the typical biomarkers of AD. [4]

1.4. Epidemiology of AD

Alzheimer's disease mainly affects the elderly. Globally, it affects about 5-10% of people over the age of 65. The incidence increases significantly with age. Furthermore, the incidence of AD in females is higher than in males, which may be related to the longer life span of females and the pathological changes in the brains of female patients in Alzheimer's disease are more pronounced than in males. However, early-onset Alzheimer's in people under 60 years of age is rare, accounting for only about 5% of all cases. [5] The disease imposes a significant economic burden on individuals, families and society, including high medical and care costs, as well as physical and psychological stress on caregivers. As the global population ages and the overall population rises, the incidence of Alzheimer's disease is expected to continue to rise. This is a huge challenge for governments and society, and requires greater investment in research, prevention and treatment of AD.

1.5. Current treatment of AD

The current treatment methods mainly include drug therapy and non-drug therapy. In terms of drug treatment, the first is cholinesterase inhibitors (such as Donepezil, cabala tine and galantamine), which can inhibit the activity of the cholinesterase enzyme and reduce the breakdown of choline in the brain. By increasing choline levels, it helps improve cognitive function and memory.

Beta-secretase inhibitors (such as Aducamabene) which targets a major pathology of Alzheimer's disease: the accumulation of beta-amyloid plaques in the brain. Beta-secretase inhibitors act to inhibiting the activity of beta-secretase and reducing the cleavage of amyloid precursor protein (APP), thereby reducing the production of beta-amyloid. This helps slow or stop the formation of beta-amyloid plaques,

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which in turn slows the progression of Alzheimer's disease. However, their effectiveness and safety are still being studied. As for the NMDA receptor antagonists, such as Memantine, are used to reduce the influx of intracellular calcium ions, NMDA inhibitors inhibit the overactivation of glutamate, while alleviating oxidative stress and apoptosis caused by overexcitation, and protect nerve cells from damage. [6] In terms of non-drug treatment, it's more about playing a supportive role. For example, memory training and daily living skills training help patients maintain cognitive abilities, and cognitive behavioral therapy (CBT) improves mood and behavior. Moreover, psychological intervention and emotional support can be provided. In terms of lifestyle, physical and cognitive health can be improved through healthy eating (such as the Mediterranean diet) and regular exercise (such as aerobic exercise and strength training). Finally, there are supportive treatments, such as educating patients and families and improving environmental safety. In general, the use of these non-drug therapies in combination with drug therapy is critical to improving the quality of life of patients with Alzheimer's disease[7] .

For the future, it may be possible to develop drugs that target the two major pathological mechanisms of amyloid plaques and tau proteins. For example, through immunotherapy, or monoclonal antibodies to remove amyloid plaques and Tau protein abnormal accumulation. Furthermore, gene therapy can be tried to influence the disease process through gene editing. [8] However, there is no effective way to cure Alzheimer's disease generally, current treatments can only help alleviate symptoms and delay disease progression, but cannot cure the root of AD.

2. Pathogenesis and Mechanism of AD

AD is called as a mysterious disease, due to the complex pathogenesis. The first involves abnormal accumulation of beta-amyloid Precursor Protein (APP) in the brain to form aggregation, which are formed by a series of enzyme digestion reactions, After being cut by the Beta-Site APP Cleaving Enzyme (BACE1) Gamma-Secretase, the short chain Aβ fragment is formed, especially Aβ42 (containing 42 amino acids) will gradually accumulate in the brain to form the insoluble fibrous structure b and self-polymerize. Gradually forming fibers which is toxic to neurons and affects the ability of communication between nerve cells. Furthermore, another significant factor is neurofibrillary tangles formed by abnormally phosphorylated tau protein. Due to the imbalance in the regulation of phosphatases and kinases related to Tau phosphorylation, the imbalance leads to excessive phosphorylation of Tau protein, which interferes with the structure and function of neurons. [9] In addition, the first two mechanism will trigger neuroinflammatory response in the brain of AD patients, the activation of microglia and astrocytes is intensified, releasing inflammatory factors, thereby damaging neurons. [10]At the same time, genetic and environmental factors will jointly affect the development of AD, such as APOE ε4 allele will reduce the ability of Aβ protein clearing, and some chronic diseases such as high blood pressure, diabetes and some bad lifestyle caused by oxidative stress mechanisms to affect brain health [11] .

3. Overview of treatment modalities

The drugs which are currently be used, have been introduced in the part2. In this overview, will describe some drugs that are still in the clinical testing and experimental concept stage, aiming to introduce more possible target points for the treatment of AD, and provide ideas for the development of effective drugs for the treatment of AD.

3.1. Monoclonal antibody

3.1.1. Anti-beta-amyloid protein (Aβ) drugs

Aducanumab is currently the only drug approved by the FDA that can achieve Amyloid-beta aggregation. The drug works by selectively binding oligomers and fibrillary amyloid aggregates instead of amyloid monomers. [12] The mechanism of the drug is binding to fibril and targeting them for microglia-mediated removal and prevent the interaction between neuroprotective amyloid monomer and neurotoxic amyloid oligomer. In phase III clinical trial, Aducanumab successfully slowed the rate of

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cognitive decline in patient. However, due to the blockage of the blood-brain barrier, the persistence of the drug is limited which limited the long-term effect. At the same time, Aducanumab can also cause side effects such as brain edema and bleeding, thus raising questions about its usefulness and safety.[13] Although there are some unknown factors, it can still considered as a promising avenue to treat AD.

Lecanemab was also received FDA approval in 2023, differs from Aducanumab, it primarily targets polymerized forms of the Aβ protein, including early soluble polymers and plaques, rather than just mature Aβ plaques. This allows Lecanemab to intervene at an earlier stage to have a more significant impact on the progression of the disease. Lecanemab neutralizes these toxic aggregations by directly binding to Aβ aggregates and stimulating the body's immune system to clear them. Thereby reducing Aβ plaque buildup in the brain, which in turn may reduce the toxic effects on neurons and slow cognitive decline.[14] In a clinical trial called CLARITY AD, patients treated with ranalizumab showed significant improvements in cognitive tests. In addition, imaging studies also showed that the drug successfully reduced the level of Aβ plaques in the brain, which demonstrated the effectiveness of the drug. However, similar to Aducanumab, some patients experienced brain edema and small bleeding, which required regular monitoring over the course of treatment.[15] Overall, it is widely believed that the accumulation of amyloid beta (Aβ) oligomers plays an important role in the cause of the disease, and immunotherapies targeting these oligomers have shown surprising results in treating AD.[16] Despite there are some unknown factors, and there is limited research and testing data on this class of drugs, it can still be considered a promising avenue to treat AD.

3.1.2. Anti-tau protein antibody drugs

Tauroxs and ABBV-181 are both monoclonal antibodies against Tau protein, and they target the core region of Tau protein MTBD (Microtubule Binding Domain) which maintains microtubule stability by binding to microtubules, which is essential for the morphology and function of neurons. They bind to tau through these specific sites, preventing the abnormal aggregation and tangling of Tau in nerve cells. It also encourages the immune system to recognize and clear these protein aggregates that are harmful to neurons. Through such a mechanism, tau accumulation is reduced, thereby reducing nerve cell damage and maintaining cognitive function. The drug is currently undergoing clinical trials to assess its efficacy, safety and tolerability in patients with Alzheimer's disease. Monoclonal antibodies targeting Tau are expected to be a new therapeutic direction for the early stage of Alzheimer's disease.[17] Such targeted pathways have the potential to become a new option for treating Alzheimer's disease, especially for those patients with abnormal accumulation of tau protein. Further verification of its mechanism of action and clinical effect will provide important data for the development of tau targeted therapy and guide future treatment strategies.

3.2. Tau protein binding drugs

LMTX, a small molecule drug, is a tau protein aggregation inhibitor. Its active component is MTC (chlorinated form of methylene blue), but LMTX is a new stable crystalline methylene sulfide ammonium salt, which can overcome the pharmacokinetic limitations of MTC, target the core region of tau protein, such as the tetramer region (four repeated sequences), inhibit its aggregation and the formation of tangles, and maintain the normal function of microtubules. Improves neuron survival and function. [18]Multiple rounds of clinical trials have shown that LMTX has shown potential to delay disease progression in some patients and may help improve memory and cognitive function in patients. At the same time, LMTX also has a high safety and mild side effects, only possible digestive discomfort, such as nausea and diarrhea. [19] Once the results of subsequent studies and trials confirm its positive effects, LMTX may become a new treatment option for tau-associated neurodegenerative diseases.

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3.3. Design antibody drug conjugation drug for improvement

3.3.1. Side effects of long-term medication

AD as a long-term disease usually requires long-term medication to manage symptoms and slow progression. However, the long-term accumulation of drugs in our bodies can cause a series of adverse reactions, resulting in systemic toxicity, affecting the function of the stomach, liver, kidneys and immune system, affecting the quality of life and health of patients[20] .

3.3.2. Advantage of ADC

An antibody drug conjugate (ADC) is a target-specific drug with a monoclonal antibody component, a connector, and a payload (drug) component. Known as a biological missile which able to release its drug at specific target sites to improve therapeutic effectiveness and limit systemic exposure to toxicity. The use of ADCs has significant advantages. Due to its precise targeting function, ADC drugs can accurately target specific pathological markers through antibodies, improve the distribution of drugs in the body, strongly kill target cells, and improve the effectiveness of drugs Furthermore, due to precise targeting, it can significantly reduce the side effects of drugs throughout the body and reduce the damage to normal cells.[21] Thus, trying to design traditional drugs into ADC drugs is also a promising future direction for the treatment of AD.

4. Conclusion

Alzheimer's disease (AD) is a complex neurodegenerative disease, and its pathological mechanism is still being explored. Despite significant advances in research over the past few decades, key pathological processes such as beta-amyloid, tau phosphorylation, and neuroinflammation have been revealed. In terms of treatment, although some current drugs have achieved certain positive effects, they are still unable to effectively solve this complex disease. Several key pathologic processes and therapeutic sites have also been revealed in the study of new AD drugs: beta-amyloid (Aβ) plaques; Beta-amyloid protein (Aβ) plaque precursor; MTBD region and tetramer region of Tau protein. Future therapeutic studies may further explore designing more advanced drugs for these specific sites or optimizing the effects of existing drugs, or even developing combination therapies. Through these studies, it is expected to provide more effective prevention and treatment programs for AD patients, improve the symptoms and delay the progression of AD patients, and improve their quality of life.

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