Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/65/2024.LA18096

Progress in Alzheimer's disease and treatment

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Abstract. Alzheimer's disease has a large disease burden on middle-aged and elderly people, and has become an important disease of clinical concern. At present, the incidence of Alzheimer's disease in China is relatively high, and the incidence rate is relatively high in the world. AD is a neurodegenerative disease that is related with ß-amyloid-containing plaques and tau-containing neurofibrillary tangles. Its symptoms include amnestic cognitive impairment and non-amnestic cognitive impairment. The curing of AD now mainly relies on NMDA receptor antagonists and Cholinesterase inhibitors. Recent researches also focus on more specific ways for curing AD. This article will provide an overview of the pathogenesis of Alzheimer's disease and its current treatment progress, and lay the foundation for further future treatment strategies.

Keywords: Alzheimer’s disease, Neuroscience, cognition.

1. Introduction

Alzheimer’s disease (AD), a neurodegenerative disease, is mostly seen in individuals that are over 65 years old, and is tightly associated with the appearance of ß-amyloid-containing plaques and tau-containing neurofibrillary tangles.

1.1. History of discovery

The term AD first came after the publication of Alzheimer’s case study in 1907. In which a woman, 51-years of age, was described to be suffering serious amnestic impairments and visuospatial difficulties. For a few decades, AD was considered to be a rare malady. However, in 1976, research revealed that AD is one of the main factors of death for the elderly. This led to greater awareness to AD, and stimulates the establishment of the National Alzheimer’s Disease Research Center program, which promotes the investment on research of the disease then on [1].

1.2. Symptoms

AD nowadays is recognized as a neurodegenerative disease that leads to dementia, causing amnestic cognitive impairment to most patients, and non-amnestic cognitive impairment in other cases [2]. Common symptoms include amnestic MCI, such as damnifications in language, working memory, or long-term memory, and non-amnestic deficits, like difficulties in reading. These problems are also often accompanied by neuropsychiatric symptoms, for example depression [3]. It can be clearly obtained that the disease does great harm to the normal functions of patients that are needed for daily life.

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1.3. Diagnosis

The diagnosis of AD includes many parts. A description of the every-day life of the patient from familiar individuals and the hypothesis of an experienced clinician is the first step [2]. Then neuropsychological testing is given for the identification of details of the cognitive impairments that the patient experiences. It also helps with the projection of the aetiology by the clinician [2]. Biomarkers can also do the job. MRI uses imaging biomarker and is often used to out rule other possible causes for dementia and reveals tissue loss. Another type of imaging biomarkers are Aß-PET tracers and can show the presence and position of the Aß plaques [4].

1.4. Epidemicity

The rate of morbidity of AD has been increasing for the last 30 years [5]. Research showed that about 98 million people suffered from the disease in 2023 in China [6]. The risk of getting the disease differs between different age groups. The morbidity rate o is 0.7% for individuals aged 60-64, whereas it is 8.8% for people from 80 to 84 years old [6]. Also, there is an evident difference in rate of getting the disease between genders. The likeliness for female individuals to get the disease is higher than male individuals. The mortality rate of the two genders shows a slightly different pattern however. Research in China showed that the rate of death due to dementia of woman in China is lower than men before 85 years (table 1) [6]. Another thing noticeable is that the mortality rate of AD of people in rural is much higher than in cities [6].

Table 1. The mortality rate of AD and other dementias in different age groups in China, 2021(1/1,000,000).

Age (years)	Male	Female	Total
60-	20.4	18.4	19.4
65-	50.3	41.0	45.6
70-	129.5	109.2	119.1
75-	337.3	313.6	324.7
80-	857.4	796.2	823.0
≥85	3001.3	3394.7	3239.3

2. The mechanism of AD

AD is a neurodegenerative disease, which means its symptoms occur due to the death or dysfunction of neurons. The process starts with the production of substrates with neurotoxicity, ß-amyloid-containing plaques and tau-containing neurofibrillary tangles. They cause the dysfunction of synapses and death of neurons and glia in the CNS. Therefore, the brain loses part of its function due to the decrease in number of functional neurons.

2.1. ß-amyloid-containing plaques

Aß plaques is a substrate that can be present throughout the cerebral cortex [7]. Its precursor, called APP, is a transmembrane protein found on neuron cell membranes. APP's main function is to help with the growth and repairment of the neurons. It has to be recycled after being used. In some cases, two enzymes, called ß-secretase and γ-secretase, cut the protein into 3 segments [8]. The segments in the middle are Aß molecules. After production, Aß molecules are excreted out of the cell, into the extracellular space. Due to is structure, the aggregation of Aß molecules happens in a high possibility. If the concentration is high enough, the molecules may form Aß-containing plaques. These plaques may get between neurons, hamper the transfer of information, and lead to other serious consequences [2].

2.2. Tau-containing neurofibrillary tangles

The formation of the other important substance, tau-containing neurofibrillary tangles, occurs inside the neurons. Tau protein is a functional protein that is usually associated with the microtubules in the cell.

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Tau binds to the microtubules and stabilizes it [9]. It is assumed that the presence of Aß plaques outside the neurons opens a pathway that stimulates the enzyme kinase to bring a phosphate group to the tau protein and phosphorylates it [10]. The tertiary structure of the activated tau protein can no longer sustain the protein's binding to the microtubule, and therefore the tau protein falls from the microtubule. The tau proteins then aggregate together, forming tau-containing neurofibrillary tangles [11]. Also, without the support of tau proteins, the normal functions of microtubules are disrupted. Therefore, the formation of tau tangles also leads to dysfunction of neurons.

3. The curing of AD

Due to its complexity and its relatedness to neurons, the treating and caring for AD patients include many aspects.

3.1. Comorbidities

Many patients suffering from AD also has a list of comorbidities. These include sleep disorders, hearing loss, visual loss, balance disorders, and neuropsychiatric problems. Treatments for these can be similar to ordinary circumstances, but what have to be taken notice is that patients with AD also suffers from cognitive impairment. Therefore, some treatments are not so recommended. Physicians must take specific conditions of the patient into account [2].

3.2. Drugs specific to AD

The present, mature, mainstream drugs for curing AD consists of two types. One is cholinesterase inhibitors (ChEI), which includes rivastigmine, donepezil and galantamine. The other is a NMDA receptor antagonist, named memantine [2]. There are also pharmaceuticals that are still under trial or just released. Including monoclonal antibodies [2].

ChEIs are mostly approved for the treatment of mild to moderate dementia due to AD, and can, based on results in clinical trials, slow down the progression of the symptoms caused by AD [2]. Acetylcholine is an important neurotransmitter in the brain, and the process of its functioning is shown to be partially damaged in AD patients. Cholinesterase is an enzyme that breaks down acetylcholine into choline and acetate after its release from the presynaptic membrane into the synapse. After that, the two products are then reabsorbed into the presynaptic cell, prepared to be synthesized again into acetylcholine. However, research showed that there is a losing of number of functional receptors on the membrane of neurons in brains of AD patients [12]. This means that a regular level of concentration of acetylcholine can no longer suffice the need for the signaling to the next neuron. Cholinesterase inhibitors reduce the activity of cholinesterase, therefore slowing down the metabolic breakdown of the acetylcholine, and allow it to remain in a relatively higher concentration in the synapse.

Memantine is approved to treat moderate to severe dementia caused by AD [2]. In a normal functioning brain, the concentration of the neurotransmitter glutamine in the synapse is tightly regulated. This ensures the normal functioning of the neurotransmitter and moreover, the signaling of synapses and neurons. However, in individuals with AD, the hemostasis of the concentration of glutamine is broken and serious consequences arise. The rising in the concentration of glutamine over activates NMDA receptors, leading to excitotoxicity, and eventually causes cell death. The drug, memantine, is an NMDA receptor antagonist and it inhibits the normal function of NMDA receptors, preventing the problem of excitotoxicity. However, due to the significance of the NMDA receptors, the intake of the drug should be in delicate control to maintain normal functioning of the receptor [13].

However, without targeting the crux of the disease, Aß plaques and tau tangles, the progression of the symptoms of AD cannot be stopped or significantly delayed. In recent years several attempts appeared, all aiming for a more effective treatment for AD. Aducanumab, a monoclonal antibody, targets a precursor of the plaques [2,14]. Another recent monoclonal antibody named Donanemab targets the Aß plaque itself by binding with molecules that only exist in the center of these plaques [2,15]. Clinical trials show relatively effective clearing of Aß plaques after using these drugs [15].

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4. Discussions

AD is a complicated disease, related with many aspects and can cause disruption to the daily life of patients and their family. Its presence is usually accompanied by ß-amyloid containing extracellular plaques and tau-containing neurofibrillary tangles. The accumulation of these neurotoxic substrates causes the neurodegenerative disease. Present curing for Alzheimer's Disease focuses on the symptoms or can only influence the indirect causes of the cognitive impairment the patients are suffering. There are also some new treatments appearing in recent years, mainly targeting the most critical molecules in this disease: Aß plaques and tau tangles. These new attempts give us a promising prospect of future curing of AD.

The development of drugs specific to AD is especially hard because the disease is located at the brain and the drugs need to find way through the blood-brain barrier. Also, as a neurodegenerative disease, the symptoms of AD cannot be reversed using ordinary methods.

Another important problem is the way clinical trials were performed. Most trails studying AD or developing AD-curing drugs use mouse individuals as experimental subjects. Due to the difference in structure of brain and molecular differences, results obtained in mice can be different from actual AD in human brains. Therefore, a replacement of subject is important for faster development of AD curing technology.

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