

Advances in Alzheimer's disease and its treatment

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disease with insidious onset. In clinical practice, comprehensive dementia is characterized by memory impairment, aphasia, recognition loss, impairment of visual and spatial skills, executive dysfunction, and personality and behavioral changes. According to the statistics, the global prevalence of dementia will be as high as 24 million, and is predicted to double every 20 years until at least 2040 [1]. The etiology of Alzheimer disease remains unclear, but most people think it is result of both genetic and environmental factors. How to cure this kind of disease has become a big trouble for decades.

Keywords: Alzheimer's disease; epidemiology; pathological features; causes; treatment methods.

1. Introduction

In 2005, according to epidemiological data acquired over recent years, the International Organization for Alzheimer's Disease commissioned an international scientist group to reach an agreement on the prevalence rate of dementia, and estimated the incidence rate of 14 WHO regions. It appears that, there were 24.2 million people suffered from dementia [2]. North America and Western Europe reached the highest prevalence of dementia at age of 60, account for 6.4 and 5.4% of the population at age of 60. Then it came to Latin America, had 4.9% proportion, and China and other developing Western Europe countries took up 4.0%. The incidence rates in every 1000 people in North America were predicted at 10.5, then Western Europe 8.8, Latin America 9.2 and China and other developing Western countries 8.0 annually. It was obviously increased with age in all these regions, especially in the seventies and eighties [1]. Besides, research shows that the incidence rate of Alzheimer's disease is expected to increase three times by 2050 [3].

The pathological feature of AD is abnormal protein aggregation, such as amyloid plaques (Amyloid beta $A\beta$). And neurofibrillary tangles (NFTs). Autophagy is an evolutionarily conserved biological process in eukaryotes that relies on lysosomes to clear damaged organelles and misfolded proteins. An increasing number of studies indicate that impaired autophagy function is involved in the pathogenesis of Alzheimer's disease [4].

Currently, it is believed that $A\beta$ the sedimentation is mainly due to $A\beta$ Excessive generation leads to reduced clearance, and the formation of NFTs is mainly due to excessive phosphorylation of Tau protein and hindered clearance of insoluble aggregates. There are numerous studies have observed impaired autophagy function in AD patients and AD animal models [5-6].

There are four main diagnostic methods for Alzheimer's disease. They were scale-based cognitive function assessment, PET, cerebrospinal fluid diagnosis, and ApoE detection of risk genes. Among them, the diagnostic test scale Mini — Mental State Examination is commonly used, that is MMSE, it can be used to assess memory function and other cognitive functions, and it is also one of the most influential cognitive deficit screening tools. MMSE has a good confidence, and PET imaging belongs to the field of molecular imaging and functional imaging. Imaging agents can be injected into the patient to visually display the synaptic function of the patient, the degree of tau protein phosphorylation, and the changes of various neurotransmitters and receptors. Cerebrospinal fluid diagnosis is an invasive examination, through the lumbar puncture, A certain amount of cerebrospinal fluid is extracted from the spinal space for detection, according to the level of cerebrospinal fluid $A\beta_{42}$, tau protein levels and normal indicators can be diagnosed with Alzheimer's disease. The diagnostic technique has a high accuracy rate of around 90%. ApoE risk gene test is to predict and infer the risk of AD by detecting the expression of ApoE gene in patients. ApoE gene test results are

divided into three categories: general risk type, low risk type and high-risk type, which can reflect the risk of AD of subjects.

In addition to the methods mentioned above, there are also emerging detection techniques. For example, through the detection of p-tau181 in serum, plasma and CSF by single-molecule array (Simoa) immunoassay, this technology brings protein detection technology to the era of Single molecule, digital detection, and can detect ultra-low abundance protein. There is also A reusable surface immune infrared sensor to detect A β and tau proteins in human cerebrospinal fluid. The key element of the sensor is an Attenuated total reflectance (ATR) crystal with a chemically modified surface that captures biomarkers from body fluids.

Another approach is to apply a DNA aptamer and antibody specific to the Tau-381 subtype to the Surface plasmon resonance platform (SPR) for concentration analysis of the Tau-381 subtype in human plasma. The detection limit was 10fmol/L. In comparison with commercial ELISA kits, the assay was found to have a 1000-fold increase in performance, while also being able to measure concentrations of 2 pmol/L that cannot be measured by ELISA [7].

There are some other detection technologies are also developing in a deeper direction and gradually maturing, but some are still in the research stage and have not yet formed systematic diagnostic measures, which are temporarily not used in clinical diagnosis.

2. Alzheimer's Disease

2.1. Causes

The pathological causes of Alzheimer's disease are currently unclear, but it is generally believed to be β - Amyloid protein deposition, neurofibrillary tangles, neuroinflammation, neuronal loss and death, etc [8-9]. The core components of insoluble amyloid plaques in the brain are β - Amyloid- β Protein, A β). Classic A β the cascade hypothesis suggests that A deposited in the form of neuroinflammatory plaques β Inducing AD by destroying neuronal cells [10-11]. A β By A β Amyloid precursor protein (APP) through β Secretory enzymes and γ Produced by the gradual degradation of secretory enzymes [12]. Tau protein is a protein within neurons that helps maintain the structure and function of neurons under normal circumstances [13-14]. The normal Tau protein is in a non-phosphorylated state and can bind to microtubules. However, in the AD state, Tau protein undergoes abnormal phosphorylation (p-Tau), causing it to lose its ability to bind to microtubules and form neurofibrillary tangles (NFTs) [15], These tangles affect the normal function of neurons, leading to neuronal death and brain degeneration [16-17]. In summary, current evidence suggests that AD is a typical "folding disease" caused by changes in the spatial conformation or folding of at least two proteins. A β Through complex interactions with Tau proteins, a large number of protein oligomers that are difficult to degrade and easy to deposit are formed, synergistically producing neurotoxicity and ultimately promoting the occurrence and development of AD [18].

2.2. Symptom

For Alzheimer's patients, the most basic symptoms are memory problems and cognitive decline. Such as forgetting where things are placed, unable to recognize the relatives around and so on. It can also be accompanied by other cognitive impairments, such as difficulty making decisions, loss of direction, and decreased language skills. With the development of the disease, there may be a situation of being unable to take care of themselves, unable to independently complete basic life operations, such as eating, dressing etc. They often suffer from hallucinations. The hallucinations of these patients are usually visual, with less auditory and even less tactile and olfactory senses [19]. In addition, as the severity of the patient's condition increases, persecution delusions and misidentification delusions will also increase, and persecution delusions will appear earlier. Patients with AD usually also suffer from agitation and apathy. Apathy usually manifested as lack of motivation, movement disorders, emotional apathy, and lack of enthusiasm, it is one of the most painful reasons for caring for AD

patients [20]. Besides, some patients may suffer from sleep disorders, like insomnia, sleepwalk and talk in sleep.

3. Treatment

3.1. Targeted drugs

Currently, acetylcholinesterase inhibitors (AChEI) are the main drugs used for the treatment of Alzheimer's disease, which are inhibitory neurotransmitters. Representative drugs for cholinesterase inhibitors include tacrine, donepezil, huperzine A, etc. Among them, tacrine has gradually withdrawn from the market due to its significant side effects. However, recently, MINARI and others have synthesized tacrine derivatives with lower side effects, which are expected to become new multi target drugs for the treatment of Alzheimer's disease [21]. Recently, YANG et al. pointed out that donepezil can be used in combination with other drugs to improve learning behavior in mice, with a much better effect than using donepezil hydrochloride alone. However, this combination can produce side effects such as vomiting and constipation. Therefore, there is still controversy over whether it is worth promoting [22].

3.2. Neural stem cell transplantation

Stem cell transplantation has intervention effects on multiple stages of the development of neurodegenerative diseases, such as repairing damaged synapses, regulating inflammatory responses, and neuroprotection. At present, the most commonly used types of stem cells for treating neurodegenerative diseases include NSCs, mesenchymal stem cells (mesenchymal stromal cells, MSCs), and induced pluripotent stem cells (induced pluripotent stem cells, iPSCs). Among them, NSCs transplantation for the treatment of AD is considered to have great potential and may play a role in multiple aspects, such as protecting capillaries and reducing A β Deposition of tau, alleviation of inflammatory reactions, and promotion of neurogenesis. Although the debate over which type of stem cells should be used to treat CNS injury patients continues, the ability of NSCs to treat various preclinical neurodegenerative disease models and differentiate into central nervous system (central nervous system, CNS) related cells has been reported. In fact, NSCs have been transplanted into patients with amyotrophic lateral sclerosis and Parkinson's disease, and have been proven to be safe and have preliminary effects [23].

3.3. Acupuncture treatment

Traditional acupuncture methods include body acupuncture, electroacupuncture therapy, acupoint embedding and acupoint injection. With the development of medical technology, acupuncture and medicine can also be used as auxiliary treatment. Studies have shown that acupuncture can regulate the release of neurotransmitters between synapses and improve the sensitivity of nervous system. It can also inhibit cell apoptosis through anti-oxidative stress damage, and inhibit cell senescence to a certain extent, thus protecting neurons [24]. In addition, when performing acupuncture, the needle of leveling and reinforcing and purging can prevent strong stimulation that the elderly cannot bear.

3.4. Graphene based nanostructures in treatment of AD

Graphene oxide (GO) has attracted considerable interest due to its good biocompatibility, high solubility and dispersity, and low cytotoxicity [25]. Considering the above excellent properties of graphene, several laboratories have shown that graphene and its derivatives show great promise in the therapeutic intervention of AD. For example, Mahmoudi et al [26]. highlighted that graphene oxide and protein coated with graphene oxide can slow down the A β fiber formation process. Notably, the wide surface area of the graphene oxide sheet was shown to block the process of beta fibrillation through amyloid monomer adsorption. Yang et al [27]. found that graphene oxide could not only inhibit the fibrillation of a- β 1-40, but also effectively eliminate advanced amyloid fibril. In addition,

Li and team emphasize that graphene oxide interacts with the aggregation mechanism of A- β 33-42, resulting in considerably smaller fibril in the presence of graphene compared to the long, intricately wound fibril in the control group [28]. Their further study [29] found that graphene oxide had a significant attenuation effect on the aggregation of A- β 33-42. In addition, they envisioned the effects of different shapes of carbon nanotubes and graphene oxide on A-beta 33-42 aggregation [30] and found that graphene oxide nanosheets, accompanied by nanotubes and nanodots, had the greatest inhibition. In addition, another study showed that graphene oxide not only effectively attenuates the aggregation of A β 1-42, but also reduces the toxicity of A β [31].

3.5. Lencanezumab

Lencanizumab is A recombinant humanized immunoglobular egg γ 1 (IgG1) monoclonal antibody that preferentially targets soluble aggregates of A β and is also active against insoluble fibril. A β pathology is closely related to inflammation, and reactive astrocytes are closely located around plaques. Astrocytes effectively engulfs dead cells, damaged synapses, and protein aggregates, playing an important role in maintaining brain homeostasis [32].

3.6. Autophagy

Autophagy is essential for maintaining neuronal cell homeostasis and function. Unlike mitotic cells, mitotic cells can relieve proteinopathy by dilution of aggregates through cell division, while highly differentiated neurons rely to a large extent on autophagy to remove insoluble macromeric albumin aggregates and maintain cellular homeostasis. Some studies have found that some autophagy related proteins in AD brain are down-regulated, which affects the pathological changes of AD. Dysfunctional autophagy will lead to the accumulation of A β and tau egg white, and the pathological changes of AD will also lead to autophagy defects, forming an evil cycle, thus making AD progressive. Generally speaking, increased autophagy in the early stage of AD helps cells adapt to in vitro and in vivo stimuli and promotes homeostasis, but increased autophagy can lead to autophagy death and eventually lead to progressive progression of AD [33].

3.7. Sports

It has been widely recognized that exercise improves memory and reduces the incidence of dementia in old age, but the mechanism by which exercise improves memory remains unclear. The activation of GABA system plays an important role in preventing neuronal overexcitation and maintaining the excitation-inhibition balance of neural networks. It has been reported that the deficiency of GABA system may be the key to the excitatory toxicity of AD hippocampal neurons. According to a study, scientists use APP/PS1 mice (AD model) and C57BL/6J mice were randomly divided into AD quiet group (APP/PS1), AD exercise group (APP/PS1+EXE), wild-type quiet group (WT), and wild-type exercise group (WT+EXE). APP/PS1+EXE group and WT+EXE group performed treadmill running for 12 weeks. Then use Y-maze and MWM were used to detect the cognitive behavior of AD model and wild-type mice, including working memory and spatial learning memorability. The result is, twelve weeks of aerobic exercise training can effectively inhibit the production of A β in the hippocampus of APP/PS1 mice, and at the same time promote the increase of PV+ neurons in the CA1 region of the hippocampus, thus improving the cognitive ability of the hippocampus of APP/PS1 mice. The decrease in the number and impaired activity of PV+ neurons in the hippocampus will lead to A certain degree of cognitive dissonance in mice. Therefore, the increase in the number and activity of PV+ neurons along with the decrease of A β deposition may be one of the mechanisms by which aerobic exercise improves the spatial memory ability of AD model mice [34]. However, this method has not applied in human body, there still need some tests before using this kind of method.

3.8. *Spirulina platensis*

It is a kind of filamentous prokaryotic cyanobacteria composed of a single row of cells, unbranched and undifferentiated cells. To reproduce by forming algal colonies. This method is going to use *Spirulina platensis* alleviates high fat diet to incline cognitive impairment in mice via the gut-brain axis. This method also uses mice to test the efficacy, so it has a same problem as 3.6, that is the safety. All mice were placed in a 12-hour light/dark cycle and fed freely for food and water. After 1 week of adaptation, they were randomly divided into 5 groups (n = 10) : (1) control group (Con) was fed normal diet, (2) model group (M) was fed high-fat (20% lard) diet (HFD), (3) *Spirulina* low-dose group (SPL), (4) *Spirulina* medium dose group (SPM), and (5) *spirulina* high-dose group (SPH). SPL group, SPM group and SPH group were fed HFD supplemented with 0.5%, 1% and 2% (w/w) *spirulina*, respectively (supplemental Table 1). Piglets fed the experimental diet were subjected to Barnes maze test and Morris water maze test after 14 weeks and 15 weeks, respectively. After 16 weeks of intervention, the mice were killed. The results appeared great effect [35]. Nevertheless, scientists should do more research to check if this method can be used in human body, whether it still have function, is there any damage may be caused in human body.

3.9. Regular inspection and monitoring

Regular examination can detect abnormalities and lesions in the body as early as possible, which can help patients receive treatment as early as possible, and is also an important way to help patients relieve symptoms.

3.10. Lifestyle management

As a major chronic disease, Alzheimer's disease also has some causes of poor living habits. Such as drinking, staying up late, smoking and so on. Therefore, maintaining good living habits, healthy diet, adequate sleep, appropriate exercise, are an essential part of a healthy life, but also an important means of disease prevention and treatment.

4. Conclusion

At present, there is no practical cure for Alzheimer's disease, so there are only a few ways to prevent it. At present, there are several common prevention methods. As with other chronic diseases, effective prevention measures for Alzheimer's disease are regular medical checkups, adequate daily exercise, and intentional training that exercises the brain or requires the brain to think. In addition, it is necessary to maintain proper social activities. Participating in social activities can help keep your brain active, such as volunteering or participating in senior college. Keeping your body and mind healthy is also a good way to prevent it. Depressed emotions such as depression, anxiety, etc. may have a negative impact on the brain, which further puts pressure on the body, leading to the occurrence of diseases. Last but not least, keep some study habits. In your spare time, you can do some reading, learn new skills, and complete some puzzle games to exercise your brain, help your brain stay active, and maintain cognitive function.

Alzheimer's disease is still a kind of disease which cannot be cured now, like cancer and Parkinson and so on. However, many research directions have emerged, and researchers are working hard on various aspects of research, some of which have made good progress. Next, we need to verify the feasibility and safety of some methods in humans to get a more reliable way. However, it is important to note that, as with most chronic mental illnesses, it is also important to be prepared for the possibility that it may not be cured. At present, it is medically and biologically possible to prevent and mitigate as much as possible. However, effective progress in the near future seems very likely. The author also hopes to see a day in the future when a cure for Alzheimer's disease is possible.

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