Pathological Mechanism of Alzheimer's Disease, Progress in Drug Development and Future Prospects

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Abstract. Alzheimer's disease (AD) is the main cause of dementia. Its complex pathological mechanisms and multifactorial characteristics make the development of treatments face great challenges. This article reviews the origin of AD, symptom treatment drugs, pathological mechanism research, drug development progress and prevention strategies, and analyzes the limitations of current clinical applications and future development prospects. The study reviewed the historical discovery of AD, especially the genetic decoding of early-onset AD (EOAD), and explored key pathogenic genes such as APP, PSEN1, and PSEN2 and their role in the Aβ cascade hypothesis. In addition, this article summarizes the development of AD therapeutic drugs, including symptomatic treatment drugs such as cholinesterase inhibitors and memantine, as well as the progress of targeted therapy based on Aβ and Tau proteins in recent years. Although new antibody drugs such as aducanumab and lencanumab have been approved for marketing, their clinical efficacy is still controversial, and their high cost and potential side effects limit their widespread application. At present, AD research is facing the challenge of theoretical hypotheses and the exploration of new therapies. The future development direction may involve more accurate early diagnosis, biomarker screening and personalized treatment strategies, in order to improve the treatment effect and improve the quality of life of patients.

Keywords: Alzheimer disease; beta-amyloid; pathogenesis.

1. Introduction

Throughout the history of human disease treatment, neurological diseases have proven to be tough enemies. Dementia, stroke, and Parkinson's disease are particularly serious dangers to human health and life. Dementia, in particular, describes an intra-individual pattern of decline in memory and thinking impairing at least two domains of cognition [1]. Globally, a new case of dementia is diagnosed every three seconds. In 2019, an estimated 55 million people were living with dementia, and this number is projected to increase to 139 million by 2050. Alzheimer’s disease (AD), a neurodegenerative disorder characterized by progressive cognitive decline, accounts for 60-70% of all dementia cases, with the fastest growth rates observed in low-income countries. In 2019, the global economic burden of AD reached $1.3 trillion, and this figure is expected to exceed $2.8 trillion by 2030. The costs primarily stem from healthcare, caregiving, and productivity losses [2]. Pathologically, the mechanism of AD primarily revolves around beta-amyloid (Aβ) , pathological tau protein, and neurodegeneration, but there is still no certain conclusion. Despite decades of research, disease-modifying therapies remain elusive, which underscores the urgency to advance diagnostic precision and mechanistic understanding, also necessitating innovative approaches to early intervention and personalized care.

2. Historical Discovery of AD and Genetic Decoding of EOAD

2.1. Breakthroughs in Early Medical Cognition

In the mid-19th century, German physician Heinrich Hoffmann argued that mental illness was a real disease, and that the patients were not morally corrupt or possessed by evil spirits, but rather that they had suffered insidious brain damage and therefore deserved proper treatment and care. This view laid a scientific foundation for the subsequent discovery of AD.

2.2. The Auguste Deter Case

In 1901, 51-year-old Auguste Deter was admitted to the "Ice Cellar" psychiatric hospital founded by Hoffmann because of his progressive cognitive decline, hallucinations, and personality changes. After four years of observation by Dr. Alois Alzheimer, he found that the patient gradually lost memory, reading and writing abilities, and social functions, and eventually passed away due to other complications such as infected bedsores and cerebellar vascular sclerosis. The hospital was unable to find an answer as to what exactly he was suffering from. After his death, slices of his brain were sent to Alzheimer's. Later the autopsy discovered amyloid plaques and neurofibrillary tangles in his brain, which first revealed the core pathological features of AD.

2.3. Disputes and Evolution of Disease Naming

To honor Alzheimer's contribution, Emil Kraepelin named the disease "AD" in his 1910 textbook of psychiatry, whose clinical symptoms manifested themselves in a gradual regression of the patient's mental faculties, memory loss, stagnant thinking, inability to action like finding the way, recognizing people, chattering at times, being silent at others, and inability to carry out any commands. Of all the symptoms, verbal confusion is the most severe, with the patient still able to speak, but also unable to understand the meaning of it, and eventually falling into a state of extreme trance. This disease is similar to dementia, but the patient is much younger and has more severe symptoms. In more accurate terms what appeared in August would actually be called early-onset AD. Besides, the current internationally used term remains AD, but the classification criteria for its clinical subtypes such as early-onset AD are still being revised [3].

2.4. Particularities of Early-Onset AD

Later, the Auguste Deter case was confirmed as the world's first case of early-onset AD (EOAD, <65 years), with a faster disease progression than late-onset AD (LOAD, >65 years) and often accompanied by significant psychiatric symptoms such as hallucinations. Subsequent studies have confirmed that approximately 50% of early-onset AD patients have a family history, suggesting the important role of genetic factors [4]. About half a century after Auguste case, research on the John Reiswig family in the 1960s first confirmed the autosomal dominant inheritance pattern of AD. In this case, among the 14 children in this family, eleven of whom were diagnosed with early-onset AD, and the clinical manifestations were highly consistent with Kraepelin's original description.

3. Advances in Symptomatic Medications

3.1. Historical Context and Catalytic Shift in AD Research

In fact, from the time Kraepelin first named the disease to the John family case, research on AD stagnated throughout the first 50 years of the 20th century, because it was taken for granted that it was part of aging itself. Neither the public sector nor drug companies were willing to fund research. It wasn't until the 1970s that this was gradually reversed. It wasn't until the 1970s that this was gradually reversed. First, academics suggested that the more plaque in the head, the worse the dementia, suggesting that plaque buildup seemed avoidable. Some data at the time showed that the prevalence of dementia among people over 65 was 4.4 percent, 65 percent of which was caused by AD. Estimating that percentage, there were about 600,000 Alzheimer's patients in the United States at the time, and the disease jumped to become the fourth leading cause of death, instantly catching the attention of the scientific community. Next was the diagnosis of AD by Hollywood movie star Rita Kevorkian, who became one of the first celebrities to publicly announce her illness. Her death sparked continued media coverage of the disease. In addition, the National Institute on Aging immediately established the national Alzheimer's Association, whose affiliations soon spread to 44 states across the country. By the mid-1980s, the association's budget had grown from an early

$0.8million to $28.9 million, and that money went directly to the development of first-generation drugs.

3.2. Cholinergic Hypothesis and the Emergence of Tacrine

Doctors at the time found that the neurotransmitter called acetylcholine was significantly reduced in the patient's brain, so they wanted to try some ways to increase the level of acetylcholine. They tried some ways to increase the level of acetylcholine, such as asking the patient eating more fish, meat, eggs and other acetylcholine-rich foods, or injecting it directly into the patients' brain. After a few attempts, scientists found that no matter how much choline they ingested, they were unable to improve their cognitive abilities [5]. To put it another way, acetylcholine is broken down by the enzyme acetylcholinesterase when it enters the brain. So, wouldn't it be enough to lower the level of acetylcholinesterase to slow down the former's reduction? The answer is that it does work. There is a drug called tacrine that has been shown in several experiments to improve cognitive performance in patients by inhibiting acetylcholinesteras. Despite side effects on the liver, short-term improvement in less than half of patients, and intolerance in 25% of patients, tacrine was approved by the FDA in 1993 as one of the first medications for AD. After that, three more medications with fewer side effects were marketed to push tacrine out of the market: Donepezil, Carabadine, and Galantamine.

3.3. Glutamatergic Mechanisms and the Introduction of Memantine

In addition, scholars have found that certain neurons in the patient's brain that interact closely with glutamate, which is also a neurotransmitter and can be stimulated to work at very low concentrations, are damaged. Alzheimer's may be related to excitotoxicity caused by high concentrations of this neurotransmitter [6]. As a result, in 2003, magnesium vajra hydrochloride was approved and marketed for the treatment of moderate to severe AD. All of these drugs mentioned above that target neurotransmitters are soothing and cannot be stopped. Reversing the disease clearly requires more precise targeted drug therapy capable of reversing the course of the disease for patients with early-onset Alzheimer's like Auguste, who developed the disease in his 50s.

4. Research on AD pathological mechanism

4.1. Disease Classification and Genetic Characteristics

Based on the age of onset, AD can be divided into early-onset AD with age under 65 and late-onset AD with age over 65. The latter also called sporadic AD because the onset is so random and isolated, but it's not completely random and genetically related, accounting for over 90% of total cases. Study shows that apolipoprotein E (APOE) gene polymorphisms are closely linked to disease risk. Carriers of the APOE4 allele are at greater risk of develpoing the disease, while APOE2 carriers face lower risk [7]. In contrast, EOAD constitutes only 5%-10% of cases, following an autosomal dominant inheritance pattern with pathogenic genes including APP, PSEN1, and PSEN2 [4].

4.2. Genetic Research Methods

Following the above mechanism, researchers can then use known DNA as a marker. Linkage analysis identifies pathogenic genes by tracking the co-segregation of chromosomal markers and disease phenotypes. This method relies on the probabilistic inheritance of DNA fragments during meiotic recombination, pinpointing candidate gene regions through analyzing marker-disease linkage in pedigrees. Due to the high variability of human genomic sequences, exclusion methods are inefficient in gene mapping. Chromosome 21 later became an early focus due to two reasons. First, because of its small size. Another reason is that Down syndrome (DS) is caused by infants having an extra copy of Chromosome 21, and many of them develop Alzheimer's-like symptoms as they get old [8]. So, throughout the 1980s, the scientific community pretty much focused on chromosome 21.

4.3. Discovery of Key Pathogenic Genes

4.3.1. Amyloid Precursor Protein (APP) Gene

In 1987, β-amyloid protein (Aβ) was identified as the main component of amyloid plaques in AD patients' brains [9]. Subsequently, the APP gene was mapped to chromosome 21, with mutations shown to cause abnormal Aβ cleavage [10]. The APP gene spans approximately 2,100 coding bases, and mutations increase Aβ42 production, promoting plaque formation [11].

4.3.2. Presenilin (PSEN1/PSEN2) Genes

In 1993, St. George-Hyslop et al. first reported that PSEN1 gene mutations located on chromosome 14 are associated with EOAD, which accounted for ~70% of all EOAD cases [12]. PSEN1 encodes a subunit of γ-secretase, and its mutations lead to aberrant enzymatic cleavage, generating excess Aβ42 [13]. Later, the PSEN2 gene located on chromosome 1 was identified, with mutations contributing to 5% of total EOAD cases [14].

4.4. Amyloid Cascade Hypothesis

Based on these genetic findings, from 1907 when Alzheimer reported the first case, to 85 years later, John Hardy finally published the simple and clear "amyloid cascade hypothesis" in 1992, positing that gene mutations leads to abnormal Aβ aggregation is central to AD pathogenesis [15]. Normally, APP is cleaved by α- and γ-secretases to produce non-pathogenic p3 fragments. Pathogenic mutations, however, cause aberrant β- and γ-secretase cleavage, generating Aβ42, which readily aggregates into toxic oligomers damaging neurons. Moreover, both Aβ40 and Aβ42 are essential for the healthy functioning of the brain, and that damage to neurons only occurs during the process of bonding into oligomers [16]. Additionally, there were some other incidents. In 2006, Kotilinek et al, erroneously reported Aβ56 as a pathogenic factor, sparking academic challenge, and it was later verified to be an instance of academic fraud.

5. Progress and Challenges in the Development of AD Drugs

AD has long posed a significant challenge in the field of drug development. The dominant amyloid cascade hypothesis posits that reducing the accumulation of Aβ plaques is a crucial therapeutic approach. Nevertheless, the journey of developing drugs based on this hypothesis has been fraught with difficulties, with numerous multinational pharmaceutical companies investing substantial resources yet achieving limited success.

5.1. Early Endeavors with γ-Secretase Inhibitors

Generally speaking, the development of a new drug has to go through the following processes, which are animal experiments, phase I, phase II and phase III clinical trials. After the whole process, only about 6% of the drugs can successfully pass phase III clinical trials in 15 years on average. To put it bluntly, every development of a new drug is an extremely high-risk, accompanied by a very high return on gambling. Initially, companies like Eli Lilly, Roche, Johnson & Johnson and others centered their efforts around γ-secretase inhibitors, trying to inhibit the production of secretase, to reduce the level of β-amyloid. But no matter which kind of inhibitors have little effect, and cause skin cancer such as basal cell carcinoma, squamous cell carcinoma and serious burden on the liver [17].

5.2. Exploration of Vaccines and Immunotherapies

After successive setbacks with the inhibitors, researchers tried to tackle the problem from a different angle. For example, Dr. Dale Schenk, a physiologist at the University of California, raised the question of whether to develop a vaccine for AD. After he injected weeks-old rats with beta amyloid, the rats that originally carried the mutated gene actually did not actually develop brain damage as adults [18]. In clinical trials, the vaccine stimulated helper T cells that triggered severe

encephalitis [19]. So many companies tried to develop a second-generation vaccine that could bypass the T cells, unfortunately, all culminated in failure.

Since neither secretase inhibition nor a vaccine worked, Lilly set its sights on a passive immunization AD vaccine, administering the antibody directly to the patient. Lilly's solanezumab, for example, has been shown in animal experiments to transfer beta amyloid into the bloodstream with excellent results. Many aged rats with car tires remembered better after six weeks of continuous use, and the drug showed some efficacy in a later phase II-III clinic [20]. Unfortunately, in the second phase III clinical trial, solanezumab still showed little difference in efficacy from placebo even in asymptomatic and mildly symptomatic gene carriers [21], result in the development failed.

5.3. Targeted Drugs for Microtubule-Associated Protein (Tau)

In response to the failure research in the plaque and the hypothesis that excessive phosphorylation of Tau protein leads to neurofibrillary tangles, research shifted towards inhibiting Tau aggregation. However, there are two other problems with the hypothesis, one is that any gene mutation related to microtubule protein phosphorylation could not be found. The second is that the researchers involved found no abnormality after removing the microtubule proteins in the rat's head, and even if the microtubule proteins malfunctioned there would be other proteins to stabilize the microtubules. In short, the theory points drug companies to another party thought, which is to block tau protein coalescence. In 2016, the same year that Lilly's solanezumab failed, a Tau drug developed by an Austrian company became the first of its kind to enter phase III clinical trials. However, the trial design had significant flaws, as there was no significant difference in efficacy between the high-dose group and the placebo group (which contained a low dose of the drug), meaning that taking four milligrams is no different than taking 100 milligrams of a drug, which is pure nonsense.

5.4. Recent Breakthroughs

Excluding the five symptomatic drugs already on the market, all of the more than 300 new AD drug developments from 2003 through 2020 have ended in failure. Many of these drugs were not even make it to clinical testing, at a total cost of more than $600 billion. It wasn't until 2021 that aducanumab was introduced as the world's first aβ antibody for Alzheimer's treatment. Earlier in 2024, a second drug, lecanemab, was also approved for marketing in China. Meanwhile, Lilly’s donanemab is also in the process of applying for marketing.

6. Current status of AD and Challenges

6.1. Limitations of Amyloid Cascade Hypothesis-Based Therapies

Current drug development for AD still relies heavily on the amyloid cascade hypothesis, yet there are significant limitations in the clinical efficacy and safety of existing drugs. In addition to being expensive to administer, another problem is that they still do not completely reverse AD. For example, aducanumab had been abruptly called off in March 2019 testing. The reason was that the medicine was about as effective as a placebo in slowing down memory loss and impaired thinking. In addition, both aducanumab and the second drug, lecanemab, require patients to undergo regular brain scans before and while taking them [22], and the latter in particular also requires genetic testing, which can lead to serious side effects if it carries ApoE4 [23]. In addition, patients may need to take anti-epileptic, antidepressant drugs in conjunction with their treatment. The overall conclusion is that although donanemab cleared plaque four times as fast as aducanumab within six months, on balance, especially in patients with moderate to severe disease, the current drug regimen is still suboptimal.

6.2. Theoretical Challenges to the β-Amyloid Hypothesis

It is still unknown whether targeting an aβ treatment that isn't necessarily the real cause of the disease will trigger other serious side effects. As a result, a growing number of scholars have begun

to question whether the amyloid cascade hypothesis is actually plausible, and the following ideas have been proposed. Type 3 diabetes hypothesis, for instance, suggesting that AD may represent "brain-specific diabetes," with insulin-degrading enzyme (IDE) dysfunction impairing Aβ clearance. However, epidemiological studies, have not confirmed a direct causal link between diabetes and AD [24]. Another example is the prion-like propagation hypothesis. This hypothesis posits that AD is related to the prion. The amyloid and tau proteins are actually formed by the accumulation of the prion. By this argument, AD might then be contagious, but the ability to transmit viruses has not been found in tests on various primates [25]. There are also a number of other points, but for now, there haven't been a final conclusion.

7. Prevention Strategies

7.1. Genetic Testing and Risk Assessment

Individuals aged over 50 years should consider genetic testing for AD-associated genes, such as ApoE (apolipoprotein E), with the ε4 allele linked to late-onset AD risk [26]. Monitoring biomarkers like inflammation markers, fasting insulin levels, hormonal profiles, immune function, blood-brain barrier integrity, body mass index, and brain volume aids in early risk identification [27].

7.2. Lifestyle Modifications

Study suggests that, long-term consumption of diets rich in vitamin D reduces risk of AD [28], so consuming foods that contain more vitamin D is a great option. Moreover, the FINGER trial showed that a multidomain lifestyle intervention can benefit cognition in elderly people with an elevated risk of AD [29]. This way of aging in excitement can all delay the rate of brain degeneration. In addition to material satisfaction and physical care, perhaps for the elderly, their psychological emptiness is also worth our attention. Active communication between two generations often gives them more purpose and meaning in life.

Comprehensive AD prevention and management demand collaboration across individuals, families, and society. Early genetic screening, healthy lifestyles, professional care, and intergenerational connection reduce risks and enhance quality of life. Future research should prioritize translational breakthroughs to address this global challenge.

8. Conclusion

AD is a complex neurodegenerative disease, and its pathogenesis involves multiple factors such as Aβ deposition, abnormal phosphorylation of Tau protein, and neuroinflammation. At present, the treatment of AD mainly relies on cholinesterase inhibitors and NMDA receptor antagonists to improve symptoms. Although targeted treatments for Aβ and Tau proteins have made certain progress, they still have problems such as limited efficacy and high costs. In the future, AD research needs to focus on early diagnosis, biomarker screening, and personalized treatment strategies to improve treatment effects. At the same time, non-drug interventions such as healthy lifestyles and neuromodulation technologies may also provide new ideas for the prevention and treatment of AD. Overall, in-depth exploration of the pathological mechanism of AD, combined with a multi-level, multi-target comprehensive treatment plan, will be the key direction to improve patient prognosis and delay disease progression.

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