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Progress in the diagnosis and treatment of Alzheimer's disease

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Abstract. This review systematically describes the advances in the diagnosis and treatment of Alzheimer's disease (AD). The core pathological features of AD are β-amyloid protein (Aβ) deposition and neurofibrillary tangles formed by hyperphosphorylated tau protein. Its pathogenesis is complex, involving the Aβ hypothesis, the Tau hypothesis, the cholinergic hypothesis and, the inflammation hypothesis, and they are significantly affected by genetic factors (such as familial AD gene APP / PSEN 1 / PSEN 2 and sporadic AD risk gene APOE ε4). In terms of diagnosis, the development of cerebrospinal fluid biomarkers (e.g., t-tau, p-tau) and imaging techniques (amyloid PET, Tau PET, sMRI, FDG-PET) greatly improves the precision of early diagnosis, differential diagnosis, and disease progression monitoring. Current treatment mainly includes symptom improvement drugs: cholinesterase inhibitors (donepezil, etc.) to improve cholinergic function, NMDA receptor antagonists (memantine) to reduce excitotoxicity, often combined but unable to change the course of the disease. The breakthrough was the anti-Aβ monoclonal antibody (e.g., Lecanemab) as a disease-modifying therapy that proved to clear A β plaques in clinical trials and significantly reduce cognitive decline in early AD patients, despite challenges such as safety (e.g., ARIA), cost, and applicable population (early only). Future research aims to optimize existing therapies, develop new target drugs (e.g., anti-tau and anti-inflammatory), explore combination strategies, improve early diagnosis capabilities, and expand treatment accessibility to achieve the goal of effectively preventing and delaying the AD process.

Keywords: Alzheimer's disease; β-amyloid protein; tau protein; diagnosis; treatment.

1. Introduction

Alzheimer's disease (AD), as a progressive neurodegenerative disease, is the most common cause of dementia, and its incidence has risen dramatically with the aging of the global population and has become a major public health challenge[1]. To effectively address the disease, Deep understanding of its complex pathogenesis (core pathological features include plaques formed by abnormal deposition of β -amyloid protein and neurofibrillary tangles resulting from tau hyperphosphorylation, And the related major mechanistic hypotheses, including the Aβ hypothesis, the Tau hypothesis, the cholinergic hypothesis, and the inflammation hypothesis, And involved significant genetic factors such as familial AD-related genes APP, PSEN 1, PSEN 2, and the major risk gene for sporadic AD APOE ε4), Also optimize diagnostic methods (e. g., the use of cerebrospinal fluid and imaging biomarkers) and review existing treatment strategies to explore new therapies.

2. The pathogenesis of Alzheimer's disease

2.1 Typical pathologic features

The typical pathological features of Alzheimer's disease are neurofibrillary tangles (NFTs) caused by abnormal deposition of β-amyloid protein and hyperphosphorylation of tau protein. Aβ plaques are the product of cleavage by β-secretase and γ-secretase, mainly including Aβ40 and Aβ42, where Aβ42 is more hydrophilic and aggregated, and the relative concentration of Aβ42 is considered important to induce the formation of Aβ amyloid fibres and readily deposit to form plaques in the brain parenchyma[2]. The pathological accumulation of Aβ not only disrupts synaptic function and intercellular signaling, but also induces pathological changes in tau to trigger AD. Tau is a microtubule-associated protein that normally regulates intracellular microtubule stability in neurons.

However, tau is abnormally hyperphosphorylated in AD to form aggregates, which disrupt microtubule structure, axonal transport function, and cytoskeleton, further triggering neuronal dysfunction and apoptosis[3]. A synergistic effect between Aβ deposition and tau abnormalities, which jointly promote neuronal damage and synaptic degeneration, eventually leads to a sustained decline in cognitive function and clinical manifestations of Alzheimer's disease. According to Li Ying, Qian Meiqi, Qiu Xue in recent studies, the levels of total tau (t-tau), phosphotau (p-tau) and Aβ42 in cerebrospinal fluid have high sensitivity and specificity for early diagnosis of mild cognitive impairment (Mild cognitive impairment, MCI) and early AD[4]. In addition, t-tau and p-tau levels associated with brain-derived serum exosomes are also proven to be used to more precisely distinguish mild AD from MCI and to predict long-term cognitive decline, showing important potential as liquid biomarkers for early disease screening and progression monitoring[5].

2.2 The main pathogenesis hypothesis

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive dysfunction and neuronal loss, whose pathogenesis is complex and has not been determined. At the present stage, four more accepted hypotheses are mainly designed. First, the β-amyloid deposition hypothesis (the Aβ hypothesis) 6. Aβ is A protein in various configurational states produced by the cleavage of amyloid precursor protein (APP) by β and γ-secretase. The amyloid plaques formed by its deposition are one of the important pathological features of AD. Aβ oligomers can directly induce synaptic toxicity, cause cellular dysfunction, activate microglia, induce an inflammatory response, and eventually lead to neuronal death. The latest study has found that soluble Aβ oligomers are more neurotoxic in AD pathogenesis, which is a key factor in inducing disease progression. Second, the Tau hyperphosphorylation hypothesis[7]. Tau is a microtubule-associated protein that plays an important role in the regulation of microtubule stability and neuronal material transport. In patients with Alzheimer's disease, Tau is abnormally phosphorylated, leading to its aggregation and the formation of neurofibrillary tangles (NFTs), which affects the stability of onlookers and the normal function of neurons[8]. NFTs first appear in the entorhinal cortex (EC) and then spread to the limbic lobe of the brain and related cortical areas. Aberrant Tau protein can damage neuronal structures, induce cell apoptosis, and interfere with neurotransmitter release, aggravating cognitive dysfunction. Studies have shown that the phosphorylation level of the Tau protein is positively correlated with the AD disease severity, and it is an important diagnostic and surveillance biomarker[9]. Third, the cholinergic hypothesis. The cholinergic hypothesis is an earlier and more accepted view in the pathogenesis of Alzheimer's disease, suggesting that the reduction of acetylcholine (Ach) is closely related to cognitive impairment. In AD, cholinergic neurons are impaired in the brain, acetylcholine (Ach) synthesis, and presynaptic membrane release function, resulting in decreased learning and memory[10]. Both animal experiments and clinical studies have shown that the damage to the cholinergic system is highly associated with cognitive decline, and that cholinesterase inhibitor treatment can also alleviate AD symptoms to some extent. Fourth, the inflammatory hypothesis. Studies show that microglia have a critical role in AD progression, being able to phagocytose necrotic neurons and Aβ deposition and maintain homeostasis in the CNS[11]. Immunohistochemical experiments found a significantly enhanced glial cell activation in the brain of AD patients, suggesting the presence of a sustained inflammatory response. Aβ can act as an inflammatory stimulator to induce the release of inflammatory mediators such as NO, TNF, and complement C3 from glial cells, promote oxidative stress, aggravate neuronal damage, and then accelerate the occurrence of neurodegeneration.

2.3 Genetic factors and high-risk genes

The onset of Alzheimer's disease (AD) has a significant genetic basis, which is divided into two main categories: rare familial AD (FAD) and the more common sporadic AD (SAD). Genetic factors not only directly contribute to some early-onset AD but also play a crucial role in the susceptibility to late-onset AD.

Familial AD (FAD) is a relatively rare form of AD, accounting for approximately 1-5% of all AD cases. The core feature is the autosomal dominant mode of inheritance, which means that if a copy of the gene for the pathogenic mutation is inherited from one parent, there is a very high risk (usually & gt; 95%) of developing the disease within a certain age range[12]. FAD patients usually develop before age 65 and are also classified as early-onset AD. The age of onset can be as early as 30 years old, but mostly between 40 and 60 years old. Pathogenic mutations in three genes are the main cause of FAD: the amyloid precursor protein gene (APP). Its mutations directly affect the production and cleavage of the Aβ peptide segment. Presenilin 1 gene (PSEN 1): located on chromosome 14. This is the most common causal gene in FAD, and hundreds of different mutations have been found[13]. Presenilin 2 gene (PSEN 2): located on chromosome 1. Its mutations are relatively rare. Although the three genes encode different proteins with different functions (APP is the Aβ precursor, PSEN 1 / 2 is the catalytic core of the γ -secretase complex), their functional mutations all eventually lead to a core pathological change: a significant increase in the production of Aβ 142 peptide (the most aggregated and toxic form of amyloid), or an abnormally elevated ratio of Aβ 142 to Aβ 140[14]. This A β metabolic imbalance is a direct driving force for amyloid plaque deposition and disease occurrence in FAD.

Sporadic AD (SAD) constitutes the absolute body of AD, accounting for more than 95% of all cases. The age of onset is usually after 65 years old (late onset). Unlike the single-gene potent pathogenic pattern of FAD, the genetic risk factors for SAD present a high degree of complexity. It is not determined by a single gene mutation, but by small-effect variants (single-nucleotide polymorphisms, SNPs) involving multiple gene loci, and has a complex interaction with environmental factors, lifestyle, and so on[15]. There are three major alleles for apolipoprotein E ε (APOE ε) (ε2, ε3, ε4). Among these, the ε4 allele is the strongest and most well-defined genetic risk factor for SAD identified to date. Individuals with the two ε4 alleles (ε4 / ε4) experienced an increase of about 12 times earlier than the most common ε3 / ε3 genotype. APOE proteins are mainly expressed in the liver and brain astrocytes and play a central role in lipid transport and metabolism[16]. The binding affinity of ε4 protein to Aβ is different from that of ε3, resulting in a significant reduction in its efficiency of Aβ clearance in the brain. The ε4 protein may prefer to promote the aggregation and deposition of Aβ from soluble monomers to insoluble fibers. The ε4 allele status is associated with an enhanced neuroinflammatory response, possibly by affecting microglial function[17]. There is evidence that APOE ε4 may affect the phosphorylation process of tau and promote the formation of neurofibrillary tangles. The APOE also plays a role in maintaining synaptic function and neuronal repair, and the ε4 isoform may have weaker functions in these aspects.

3. Diagnosis and biomarkers of Alzheimer's disease

3.1 Cerebrospinal fluid (CSF) markers

The expression changes of Alzheimer's disease (AD), the two core biomarkers: β-amyloid (Aβ) and tau, in body fluids, have become an important basis for clinical diagnosis and disease progression prediction. Aβ is an isoform produced by the lysis of amyloid precursor protein (APP) under the action of α, β, and γ secretases. The most common are Aβ40 and Aβ42, of which Aβ42, although accounting for only about 10% of the total Aβ, is more neurotoxic. Its deposition level is closely related to the onset of AD[18]. The study shows that the reduced level of Aβ42 in cerebrospinal fluid (CSF) reflects the degree of Aβ deposition in the brain, and the Aβ42 / Aβ40 ratio has higher sensitivity and specificity in distinguishing AD from normal control. Another key indicator associated with Aβ is the Aβ42 / Aβ40 ratio, which distinguishes more between AD patients and the normal population than a single Aβ42 concentration[19]. At the same time, abnormal phosphorylation of Tau leads to the formation of neurofibrillary tangles (NFTs), which is another typical pathological feature in AD. The level of total tau (t-tau) in CSF reflects neuronal and axonal damage, while increased phosphorylated tau (p-tau) is closely associated with increased NFT load. Multiple systematic analyses showed that t-tau and p-tau levels in CSF were higher than in the normal population and

were positively correlated with cognitive dysfunction. In addition, although the plasma Aβ and tau levels fluctuate due to blood-brain barrier factors, in some people, such as those with Down syndrome and familial early AD, there is a certain clinical correlation, especially the plasma t-tau increase in the cognitively normal population, and future development of mild cognitive impairment (MCI) has predictive value[20]. In addition, the combination of various markers such as Aβ42 / Aβ40 ratio, t-tau / Aβ42 ratio, and p-tau / Aβ42 ratio in CSF can significantly improve the sensitivity and specificity of early diagnosis of AD. With the progress of proteomics and metabolomics technology, the integrated application of multiple markers will provide a more solid foundation for the early screening, typing, and precise intervention of AD.

3.2 Imaging markers

Imaging techniques are a key tool for the diagnosis of Alzheimer's disease (AD) and the types of dementia. Amyloid PET imaging allows in vivo visualization of specific radioactive tracers to bind to Aβ plaques in the brain (A+) to achieve visualization of AD core pathology (amyloid deposition). Positive results strongly support a pathological diagnosis of AD, especially in distinguishing AD from other types of dementia (e. g., vascular dementia) [21]. Tau PET Another type of tracer (such as MK-6240) is used to show the distribution and number of neurofibrillary tangles (NFTs) formed by tau aggregation (T+). Its signal intensity is highly correlated with the degree of cognitive impairment in patients, and it is brain region-specific (e. g., temporal lobe), which is a powerful tool for assessing disease stage and monitoring progression[22]. Structural magnetic resonance imaging (sMRI) clearly shows structural changes in the brain, which are typically characterized by atrophy of the medial temporal lobe (especially the hippocampus and entorhinal cortex), which extends later to the associated cortex. The sMRI is mainly used to assess neurodegenerative damage (N+) and to exclude other structural etiologies (e. g., stroke, tumor) that may lead to dementia. Fluoro-2-deoxyglucose PET (FDG-PET) reflects neuronal activity levels by measuring the rate of brain glucose metabolism. AD patients are characterized by decreased metabolism (N+) in the posterior cingulate / precuneus and temporoparietal cortex, which reflects synaptic dysfunction and decreased neuronal activity, and helps to distinguish AD from frontotemporal dementia (the latter is often characterized by decreased frontal metabolism) 23. Functional magnetic resonance imaging (fMRI), which detects functional brain activity, resting-state fMRI (like analyzing the default mode network DMN) can detect functional connectivity abnormalities in early AD, and task-state fMRI can assess changes in brain activation related to specific cognitive tasks (such as memory). Currently, fMRI is mainly used in research fields, and its clinical application potential is still being explored[24].

4. Review of treatment strategies for Alzheimer's disease

4.1 A cholinesterase inhibitor

At present, the approved treatment drugs for Alzheimer's disease (AD) are all symptom-improving, mainly suitable for moderate to severe patients, and with limited efficacy. Among them, cholinesterase inhibitors (e. g., donepezil, carbamazepine, galantamine) are the core category of clinical applications. The mechanism of action is to inhibit the activity of acetylcholinesterase (AChE), thereby reducing the degradation of the neurotransmitter acetylcholine (ACh) in the synaptic cleft. This mechanism aims to partially compensate for the severe ACh deficiency in basal forebrain cholinergic neurons loss, dysfunction, and improve neuronal information transmission between neurons[25]. In terms of efficacy, these drugs can lead to mild to moderate improvements, mainly in cognitive functions (such as memory, attention, and orientation), daily activities, and behavioral symptoms (such as indifference and agitation). Notably, the indications for donepezil and carbamazepine can extend to severe AD. However, the core limitation of cholinesterase inhibitors is their inability to prevent or reverse the neurodegenerative process of AD, only for symptomatic treatment. Cholinergic side effects are common, including digestive system reactions (such as nausea, vomiting, diarrhea, loss of appetite), bradycardia, and muscle cramps[26].

4.2 As for NMDA receptor antagonists

The brains of patients with middle and late stages of Alzheimer's disease often fall into a "signal storm", where excess glutamate continuously stimulates NMDA receptors on the surface of neurons. Normally, NMDA receptors, like smart door locks, allow calcium ions to enter only when neurons are excited, promoting learning and memory[27]. But in the diseased state, it is like a jammed gate, leading to a persistent influx of calcium ions and an "induced excitotoxicity." As a non-competitive NMDA receptor antagonist, memantine has a unique mechanism of action: it is like a "portal regulator" that selectively binds to the magnesium ion sites inside the receptor, neither completely blocking signals (preserving basic cognitive function) nor preventing calcium flooding (protecting neurons). Clinical data showed that about 50% of moderate to severe patients who took memantine for 6 months worsened in cognitive tests (e. g., ADAS-cog), and their daily living ability (e. g., dressing and eating) increased by 20%28. However, it should be clearly realized that it cannot remove the pathogenic culprit (Aβ plaque, Tau tangle), and the efficacy decreases with the course of the disease, so it is often combined with cholinesterase inhibitors (such as donepezil) to form a "twin engine" symptomatic treatment plan.

4.3 Anti-Aβ drugs

The development of anti-Aβ drugs is based on the amyloid cascade hypothesis. —— abnormal aggregation of β amyloid (Aβ) in the brain to form soluble oligomers (most toxic), insoluble plaques, triggering neuroinflammation and Tau phosphorylation. These drugs are genetically engineered monoclonal antibodies that can accurately identify different forms of Aβ: Akamab (Aducanumab), targeting fibrous Aβ aggregates to recruit immune cells (microglia) by combining plaque surface antigens; Lecanemab, which specializes in soluble Aβ fibrils (toxic oligomer precursor) to block damaged neuronal synapses. The pivotal phase III clinical trial (Clarity AD) showed that cognitive decline decreased by 27% (CDR-SB scale) and 59% less plaque in early Lecanemab patients[29]. However, about 21% of patients had ARIA side effects (amyloid-associated imaging abnormalities), presenting with brain edema (ARIA-E) or microbleeding (ARIA-H), especially in those with ApoE 4 carrier[30]. To make matters worse, these drugs are only effective in early patients, cost $26,500 a year, and require monthly intravenous infusion and regular MRI monitoring, reflecting the dilemma behind "breakthrough therapy."

5. Summary

The pathology of AD is complex, involving an intertwined network of Aβ, tau, and neuroinflammation. Accurate diagnosis based on biomarkers (CSF and imaging), especially the early identification of patients with asymptomatic or mild symptomatic stages, is the key to implementing effective disease-modifying therapy. Conventional cholinesterase inhibitors and NMDA receptor antagonists can only relieve symptoms and cannot alter the disease course.

A breakthrough in disease-modification therapies represented by anti-Aβ monoclonal antibodies (such as Lecanemab, Donanemab) has been demonstrated for the first time in a large phase III trial, showing that they can significantly remove Aβ plaques and slow cognitive and functional decline in patients with early AD, marking a new era of AD treatment. However, the absolute magnitude of efficacy, safety management (especially ARIA), treatment costs, and long-term benefits still need ongoing attention and research. Although the development of anti-tau drugs and immunomodulatory therapies is challenging, it is still an indispensable direction, and multi-target combination therapy is expected to be a more effective strategy in the future.

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