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Recent progress in the pathology, diagnosis, and treatment of Alzheimer's disease

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Abstract. Alzheimer's Disease (AD) is one of the prime cuases of dementia, responsible for 60% to 70% of cases worldwide, according to the World Health Organization (WHO). Unfortunately, numerous research challenges still remain for this disease, which poses a great threat to human health worldwide, especially in the elderly population. Scientists are still struggling to find the pathogenesis and pathogenic mechanisms of AD, and while research for new tests and novel drugs is ongoing, it faces a high failure rate. This article will summarize some remarkable results to date and discuss future research directions.

Keywords: PET scanning, Alzheimer's Disease, Amyloid-beta (Aβ), Synaptic Dysfunction

1. Introduction

AD is a progressive neurodegenerative disease that located in the central nervous system and primarily occurs in presenile and elderly populations. The amount of people who suffer from AD cases among the whole world is continuously rising, especially among the elderly group. According to a report published by the Alzheimer's Association in 2015 the rate of getting AD among the elderly population in the United States will increase from 11% to 16% by 2050 [1]. This rising trend is developing in the aging population worldwide, not only in the United States. AD can cause several complications, including but not limited to depressed mood, memory loss, decreased ability to live, and ultimately, death, at the end. Based on the report of Alzheimer's Association in 2022, 33.3% of the elderly died from AD or other dementia, and AD ranked at the seventh leading cause of death in the US during 2021-2022 [2].

As a disease with slow and insidious onset, the pathophysiological process of AD may begin much earlier the formal diagnosis of dementia [3]. The long development process of AD can be summarized as follows: the preclinical stage, mild cognitive impairment (MCI), and dementia. The clinical manifestations of AD include aphasia, apraxia, agnosia, cognitive decline, mental disorder symptoms, behavioral disturbances, declination in living ability, and memory impairment. The level of deterioration in cognitive and physical functions manifests in different symptoms at different stages. The etiology, diagnostic criteria, and treatment methods of AD are complex puzzles that have not yet been completely resolved. Therefore, developing a more comprehensive understanding of the etiology, pathogenesis, and biomarkers of AD through research, detecting the possibility of AD as early as possible or even in advance, developing tactics for AD prevention in the preclinical stage, and treatment methods with a substantial curative ratio is essential to reduce the prevalence, mortality, and medical burden of AD.

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2. Pathology

2.1. Amyloid-beta accumulation

Amyloid-beta (Aβ) production can be broadly summarized as follows: β-secretases cut amyloid precursor protein (APP) at β-sites Asp1 and Glu11 to produce C-terminal membranes with 89 or 99 amino acid fragments attached (C89, C99). BACE1 is the predominant β-secretase; however, recent studies suggest that BACE2 and cathepsin B should also be considered as additional β-secretases [4,5]. C89 and C99 were subsequently cut by γ-secretases, a multi-subunit protease complex assembles by presenilin1 (PS1), presenilin 2 (PS2), anterior pharynx defective 1 (APH-1), presenilin enhancer 2 (PEN-2) and nicastrin (NCT), in the transmembrane domain, and cleaved to produce Aβ1-40/1-42 and Aβ11-40/11-42 [6-11]. It was found that mutations in APP, progerin, apolipoprotein E (APOE4), and abnormal levels of neuropeptides may contribute to plaque formation of Aβ [12,13]. Aβ accumulation may contribute to impaired synaptic plasticity and neuronal cell death, resulting in tau hyperphosphorylation, excitotoxicity, and the generation of ROS. Thus, Aβ acts as a critical component in AD pathology and has a great potential to become a major direction for research on AD etiology as well as targeted drugs.

2.2. Neuroinflammation

Aβ precipitation and neuroinflammation are closely interrelated. Aβ precipitates activate Toll like receptors (TLRs) and immune cells, such as microglia and astrocytes. Prolonged activation if these cells produce pro-inflammatory cytokines of the IL-1β family, which increases inflammation. Tiina M Kauppinen et al. injected Aβ peptide into the brain of hAPP(J20) mice and observed the effect of PARP-1 on Aβ-induced microglia activation. Their results demonstrate that Aβ can induce microglia activation by an unknown mechanism, and that PARP-1 inhibition is able to block Aβ-induced microglia responses without impairing microglia phagocytosis of Aβ peptide [14]. Jill A White et al. treated rat astrocytes with oligomeric Aβ and found that it induces high levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1), iNOS, nitric oxide (NO) and TNF-α, leading to a significant inflammatory response [15]. Aβ also induces neuroinflammation and enhances NO synthesis, which makes Aβ plaques more difficult to be cleared by microglia, and even increases Aβ plaque formation, and inhibits synaptic plasticity [16]. Thus, Aβ induces neuroinflammation and other negative effects, and the generation of pro-inflammatory cytokines (occur in neuroinflammation), in turn, leads to increased Aβ plaques, which created a vicious cycle.

2.3. Mitochondrial dysfunction

Mitochondrial dysfunction is caused by impaired mitochondrial cytoarchitecture as well as altered electrochemical gradients. Ongoing fission and fusion events impact the size and number of mitochondria. Both mitochondrial fission and fusion proteins (including DRP1, Mfn2, OPA1, etc.) are vital elements during these processes [17]. Researches have shown that the expression of almost all mitochondrial fission and fusion proteins ia altered in the brains of patients with AD [18-21]. Although the reasons behind these changes and how they lead to structural mitochondrial damage are not clear, it is notable that the reduced number of mitochondria in biopsied brains is accompanied by a significant decline in mitochondria length but an increase in width, leading to an overall swollen apprearance of mitochondria.

Mitochondrial dysfunction leads to a decrease in ATP production efficiency but an increase in reactive oxygen species (ROS) production efficiency, a high-energy phosphate compound that provides energy supply for cellular life activities. ROS are chemically reactive oxygen-containing chemicals, and an increase in ROS can cause oxidative stress and severe cellular structure damage. And the decrease in ATP and increase in ROS due to mitochondrial dysfunction may be the main cause of the oxidative imbalance in AD [22,23]. In turn, research has shown that mitochondrial dysfunction is a significant sign for the early stages of AD [24]. Mitochondrial dysfunction may also lead to other adverse effects,

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such as calcium overload and dysregulation of calcium homeostasis in the endoplasmic reticulum (ER) [25].

2.4. Synaptic Dysfunction

Synaptic Dysfunction shows a strong correlation with cognitive decline in AD patients. It is a more obvious indicator of cognitive deficits than neurological death [26]. Synaptic Dysfunction is associated with oxidative stress, ROS, Aβ, hyperphosphorylated tau protein, loss of mitochondrial function, and altered metal homeostasis, forming a complex cycle [27].

Soluble Aβ peptide oligomers prompt synaptic loss. Aβ triggers cytoplasmic $Ca2^{+}$ elevation, abnormal redox and downstream pathways activation [28-30]. Oligomeric Aβ disrupts glutamate uptake and activates astrocyte glutamate to increase extrasynaptic domain glutamate levels. This leads to excessive activation of eNMDARs and mediates excitotoxicity, producing excess amount of reactive nitrogen species (RNS) and ROS. Furthermore, excess RNS and ROS lead to abnormal oxidative reactions in proteins, resulting in synaptic damage [31-37].

Tau protein may be also involved in the development of synaptic dysfunction. Tau is a type of microtubule-associated protein (MAP) which occurred mainly in CNS neurons' axons [38]. Its main function is to act together with other MAPs to help and promote microtubule (MT) assembly [39,40]. Under pathological conditions of tauopathies, including AD, tau protein can hyperphosphorylated, detach from microtubules, and form soluble aggregates and insoluble filaments in specific areas of the brain, eventually forming neurofibrillary tangles (NFTs) [41,42]. Compelling evidence demonstrates that excessive activation of extra-synaptic NMDARs by oligomeric Aβ leads to increased p-tau levels, indicating Aβ induced tau hyperphosphorylation. Hyperphosphorylated tau interacts abnormally with the mitochondrial cleavage protein Drp1 in brain autopsies from AD patients, revealing that tau may actively involve in Aβ-induced mitochondrial dysfunction. However, further research is required to discover the exact mechanism [43,44]. Additionally, Jadhav et al. indicated that presynaptic tau protein is associated with synaptic loss and synaptic failure and that low levels of presynaptic protein may be relevant with a growing number of NFTs [45]. Other studies have also demonstrated that tau fragments can diffuse across synapses and affect postsynaptic neurons, leading to neurogenic fiber degeneration with implications for synaptic function [46].

3. Diagnosis

3.1. PET

Positron Emission Computed Tomography (PET) is a relatively advanced imaging technique in modern clinical examinations. PET technology has also demonstrated unique advantages in the examination of patients with neurological and psychiatric disorders, and has a great future prospect for the diagnosis of AD, treatment planning, and assessment of disease progression in ongoing studies. [47]

PET works by labeling a substance, such as glucose, which is essential to the metabolism of biological life with short-lived radionuclides. These nuclides are capable of releasing positrons during decay and annihilate upon encountering one, resulting in a pair of photons with an energy of 511 KeV. A highly sensitive camera will capture this pair of photons and obtain a three-dimensional image of the aggregation of the labeled substance in the organism, reflecting its metabolic activity through calculation and analysis [48].

The use of Aβ deposition levels, tau aggregation, and neuroinflammation as PET tracers in the biomarker of AD is the dominant direction in current research, which targets the role PET imaging can play in AD detection.

3.1.1. 11C and 18F labeled Aβ tracers. In 2004, Klunk et al. found that 11C-labeled Pittsburgh compound B ([11C] PiB), a radioligand, was able to diagnose mild AD in patients by detecting higher levels of ligand residues in regions such as the frontal and temporoparietal cortices [49]. Current studies have shown that PiB PET may also be applicable to the diagnosis of mild cognitive impairment (MCI,

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mid-AD) [50,51] . The increase in amyloid load is the basis of PiB PET. However, significant elevations in amyloid load are not universal in MCI patients. Therefore, 11C-labeled tests for amyloid deposition levels are not a strong indicator in the diagnosis of MCI [52, 53].

The development of three 18F-labeled Aβ tracers, [18F] florbetapir, [18F] florbetaben and [18F] flutemetamol, has improved the detection capability of PET scanning in MCI patients [47]. Compared to [11C] PiB, 18F-labeled tracers have demonstrated advantages in recent studies with longer half-life, higher sensitivity and specificity, higher brain kinetics, and higher cost-effectiveness [47,50,52,54,55].

The extent to which the results from PET measuring Aβ deposition are reliable and valid is controversial, and this assay has limitations [56]. This is because the association of Aβ load with patient cognitive awareness, hippocampal atrophy, brain atrophy, the rate and velocity of Aβ deposition, and the sensitivity to amyloid-positive thresholds varies between patients at different stages, which are all possible influencing factors and should be a future research direction to improve the benefits of PET measurements in AD diagnosis [57].

3.1.2. Generation development in tau tracers. The first-generation tau tracer, THK tracers (especially the newer versions [18F]THK5351 and [18F]THK5317), have shown exceptional capability to differentiate MCI patients from healthy patients, with particularly high retention in temporal brain regions, along with good pharmacokinetic profiles [58]. [18F]MK-6240, a second-generation tau tracer, exhibited high binding and affinity to tau deposits [47]. Another type of second-generation tau tracer called [18F]PI-2620 was able to demonstrate tau binding in more regions, including the parietal and temporal lobes, providing more possible foundation for diagnosis. It also shows high binding and affinity, and improes the lack of off-target binding which is the shortage of first-generation tau tracers [59, 60].

In contrast to PET assay studies for amyloid deposition, there has been little progress in the research of tau aggregates as a biomarker and its use in AD detection [47]. Because tau is located inside cells, the ligands used in the assay need to have the ability to cross multiple layers of barriers. Additionally, tau aggregates are less concentrated throughout the brain than Aβ deposits, so the ligands also need to possess greater specificity than Aβ tracers [47]. Based on the current research progress, these ligands show relatively good prospects in AD diagnosis.

3.1.3. TSPO tracers for neuroinflammation. Translocator protein 18 kDa (TSPO) is present in glial cells and ventricular membrane cells [47]. It has been shown that in the presence of neuroinflammation, microglia are activated, and TSPO levels are significantly upregulated [61]. This phenomenon demonstrates that the detection of activated microglia by TSPO can measure neuroinflammation [62].

The first-generation TSPO tracer, [11C]PK11195, has been found to show a decrease in microglia activation in the pre-AD period, but an increase in microglia activation in the subsequent disease progression [63, 64]. This phenomenon was later called the bimodal hypothesis. Although [11C]PK11195 is the most well-studied tracer, it also has technical limitations due to its very short half-life, low uptake, low signal-to-noise ratio, high non-specificity, and problems with suboptimal modeling [65]. The second-generation tracers had shown a remarkable improvement within the signal-to-noise ratio and binding affinity [66]. These studies suggest an explanation for the bimodal hypothesis of AD neuroinflammation by combining the results of several studies (the second-generation tracer [18F] DPA-714 and the first-generation tracer [11C] PK11195): the peak of activated microglia in early patients serve a protective purpose of clearing Aβ deposits, whereas the later peaks are deleterious [63]. However, the second-generation TSPO tracers also have the limitation that they exhibit high sensitivity to different binding affinity patterns due to single nucleotide polymorphisms (SNPs) in the TSPO gene. Testing for these genetic polymorphisms is unavoidable in the detection of neuroinflammation using TSPO [47].

3.2. MRI

Magnetic Resonance Imaging (MRI) is a non-invasive imaging technique to visualize the internal structure of human body without exposing the patient to radiation. It provides high resolution images of

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body parts, especially soft tissues, by detecting and presenting the internal body structure by using energy with different attenuation released by nuclear magnetic resonance of nuclei [67].

The advantage of MRI testing in the clinical diagnosis of AD is its ability to measure neurodegenerative atrophy in different parts of the brain. Brain atrophy in AD patients starts in the medial temporal lobe (internal olfactory cortex and hippocampus), then spreads to the inferior temporal lobe and parietal limbic cortical regions, and finally to the multimodal joint neocortex, leading to the transformation from MCI to dementia [68]. MRI can detect changes in specific locations involved in brain atrophy, such as cortical thinning in the lateral and medial parietal, posterior cingulate and lateral temporal cortices, as well as volume atrophy in the hippocampus [69]. These changes are biomarkers of AD and can provide valuable evidence supporting the diagnosis of AD.

3.3. Fluid Diagnosis: CSF & Blood

Biomarkers, a crucial part of AD pathology, largely contribute to the clinical diagnosis of AD, especially in the examination of body fluids (CSF and blood).

3.3.1. CSF. Cerebrospinal fluid (CSF) testing is a diagnostic method which can help diagnose disease by examining changes in the composition of the specimen under pathological conditions. Aβ42 and Aβ42/Aβ40 ratio are important biomarkers in AD and prodromal AD, and their average level of change is about 50%. Their changes in these biomarkers reflect individual differences in brain amyloidosis and Aβ production or secretion, which are consistent with the results of Aβ tracers in PET. High T-tau and P-tau indicators are also pathological traits of dementia and prodromal AD, with an average change level of about 250%. However, T-tau values can change in many neurodegenerative diseases, depending on the severity of the neurodegeneration or lesion, wherase increases in P-tau can only occur in AD. Neurogranin is a promising biomarker that has emerged in recent studies and may be specific enough to meet the heterogeneity requirements of late-onset AD pathology. High neurogranin can reflect the degeneration of dendrites that characterizes the pathology of AD and prodromal AD [70].

3.3.2. Blood Testing. Blood tests involve drawing blood and analyzing the composition of the sample to detect lesions or other abnormalities in the body. The application of blood tests in AD's clinical diagnosis is a new breakthrough, and further studies are needed to fully understand their potential benefits and limitations, thus providing a stronger basis for the diagnosis of AD. Studies have shown that reduced Aβ42/Aβ40 ratio and high APP669-711/Aβ42 ratio are associated with positive brain amyloid and may be useful as a screening technique for the detecting brain amyloidosis. Increased plasma Tau is a biomarker for acute neuronal injury, including AD and some other neurological diseases; High plasma neurofilament light (NFL) is a pathological marker for AD and prodromal AD, but like tau, is not specific for AD [70]. More research is needed to optimize the use of blood tests in AD diagnosis and to identify additional biomarkers with greater specificity.

4. Treatment

As the most direct means to interfere with the progression of AD and potentially reducing its prevalence of AD at its source with preventive effects, the treatment of AD has been a topic of great interest and a major difficulty in research. The incomplete understanding of the pathology has led to stagnation in the development of targeted drugs. Due to its insidious onset and continuous progressive development, the pathological changes caused by AD may begin long before symptoms occurred, which makes the detection and treatment of the underlying pathology more difficult. The following sections summarize the existing research progress and the outlook for the future.

4.1. Drugs

Drugs which have been currently approved by the Food and Drug Administration (FDA) in the US include donepezil, rivastigmine, and galantamine are acetylcholinesterase inhibitors. These drugs are molecularly targeted to amyloid and tau proteins and are effective in patients who are in the mild to

moderate stage of AD [71]. Memantine, an NMDA receptor antagonist, can treat moderate to severe AD by diminishing the neuron excitotoxicity due to excessive glutamatergic transmission. In addition, several drugs targeting cholinergic or glutamatergic neurotransmission have been approved, but they can only have a palliative effect [72]. Numerous recently developed drugs are still in clinical trials, but unfortunately, many of them have been declared as failures because they are toxic to other parts of the body, or have no effect on the improvement of cognition or slowing down the development of AD [73].

4.2. Gene Therapy

Research has shown a close correlation between the APOE gene, presenilin 1 & 2, mutations in β amyloid precursor protein and the pathogenesis of AD [74,75]. The result demonstrates that gene mutations contribute to the pathogenesis of AD, reparing the gene defect could potentiall prevent the onset of AD [Khan]. Katsouri, L. et al. successfully injected Peroxisome proliferator-activated receptor gamma coactivator 1-alpha using a viral vector [76]. Rafii et al. demonstrated the feasibility of Adeno-associated viral vector (serotype 2)-nerve growth factor (AAV2-NGF) delivery, but gene targeting is still needed to derive clinical results [77]. More therapeutic options for AD centered on gene editing technology are still under investigation.

5. Conclusion

As a greatly lethal and complex neurodegenerative disease, AD has attracted the attention of scientists around the world. Research on the pathology and pathogenesis of AD is centered on Aβ accumulation, which interacts with other biomarkers to cause oxidative stress, neuroinflammation, mitochondrial dysfunction, synaptic dysfunction and other adverse effects, leading to further deterioration of the disease. PET scanning has shown promise in the clinical confirmation of AD, and tracers adapted to different biomarkers are being updated in research. MRI and fluid testing also play a supporting role. The development and experimentation of targeted drugs have never stopped, and gene therapy has shown unique advantages. Understanding specific pathogenetic mechanisms of AD under all kinds of biomarker, improving the defects of diagnostic tools, and continuing the search and experimention for new therapeutic tools will be the future direction of research.

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