Diagnostic indexes and pharmacological treatment of Alzheimer's disease

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Abstract

The most sensible and scientific way to control Alzheimer's disease (AD) is to diagnose and treat it early and change lifestyle and diet, so diagnostic modalities rely primarily on imaging analysis of biomarkers and examination and evaluation of serum and cerebrospinal fluid to determine AD type and disease progression in patients by several characteristic biomarkers (e.g., protein dysfunction, oxidative stress, metal ion vascular disease, mitochondrial population changes). However, there are preferences for different biomarkers in the aspect of inspection cost and patient type. As one of the signature pathologies of AD, β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) plays a crucial role in diagnosis and treatment. The difficult transmission of neurotransmitters in the synaptic gap caused by Aβ deposition is the breakthrough point for treatment and detection, which also means that detecting Aβ's specific PET ligand in cerebrospinal fluid is more meaningful. For treatments, APP-making BACE1 becomes the key point in the AD clinical treatment. The review summarizes the diagnosis and treatment of AD based on BACE1's mechanism and the process that causes AD.

Keywords: Alzheimer's disease, tau, cerebrospinal fluid, Aβ, β-site amyloid precursor protein, BACE1.

1. Introduction

As the aging of the world's population increases rapidly, the prevalence rate of Alzheimer's disease, which is the most common reason for dementia, is getting higher. Alzheimer's disease (AD) is defined as a slowly progressive neurodegenerative disease. The diagnostic approach of AD depends critically on two typical pathological processes: β-amyloid plaque deposition and neurofibrillary tangles (NFT) of hyperphosphorylated tau(p-tau), postmortem evaluation of brain tissue and bio-imaging are demonstrate how effective these diagnostic indexes are for both processes. Currently, although trials are underway, there is no way to cure Alzheimer's disease completely. However, there are two main types of drug treatment targeting symptomatic therapy, which only improves memory and alertness rather than increases life expectancy and overall progression of AD. Cholinergic transmission through the brain is damaged due to several physiological processes of AD that destroy Ach-producing cells, so cholinesterase inhibitors can block cholinesterase enzymes from breaking down Ach, which results in growing levels in the synaptic cleft. Another one is non-competitive NMDA receptor antagonists that can prevent the over-activation of NMDAR, leading to increasing levels of influx Ca2+, therefore retard cell death and synaptic dysfunction[1]. In the future, there are also many clinical pharmacological directions for pathologies of AD. For example, β-site amyloid precursor protein (APP) cleaving enzymes 1 (BACE1) acting by cutting APP and relative protein to retard the deposition of β-amyloid plaque is a promising research direction[2]. The purpose of this review is to generalize and summarize diagnostic and therapeutic methods of Alzheimer's disease and to highlight recent developments in the mechanism and effect of BACE1 inhibitor drugs in clinical trials [3].

2. Alzheimer's disease biomarker

Long before 2014, a study showed that cerebrospinal fluid(CSF)as a qualified and standardized biomarker of AD proved that it helps predict and detect the progression of AD when it works with bio-imaging[4]. Moreover, the main biomarkers used in AD studies can be divided into three binary categories based on the underlying pathophysiological nature[5].

First, according to one pathological process fibrillary Aβ deposition, high ligan retention on amyloid PET, and low CSF Aβ42 are the most powerful biological indicator[5]. However, their clinical application is different; amyloid PET testing has better sensitivity (96%) and specificity (90%) than CSF Aβ42 testing, which has a diagnostic accuracy of about 85-90%[6]. However, the cost of an amyloid PET test is much higher than that of CSF Aβ42 thus there is another problem of choosing what type of PET ligand (florbetaben, florbetapir, flutemetamol) is more suitable for patient testing[6]. At the same time, the risks of lumbar puncture surgery must also be considered.

Second, Jack also revealed that "biomarkers of tau

pathology (neurofibrillary tangles) are elevated CSF phosphorylated tau (p-tau) and tau PET."[5]. Because neurofibrillary tangles (NFT) of hyperphosphorylated tau(p-tau)is a signature pathology of AD, tracing tau PET is effective in locating the place where NFT occurs and thus diagnosing AD.

Third, the last category Jack mentioned is "Biomarkers of AD-like neurodegeneration or neuronal injury CSF total tau (t-tau), F-fluorodeoxyglucose (FDG)-PET hypometabolism, and atrophy on structural MRI in regions characteristic of AD"[5]. They are another use of tau pathology. Otherwise, neuropathy ologies require molecular evidence, so position emission computed tomography (PET) structural MRI, FDG-PET, amyloid PET, tau PET, and other relative bio-imaging techniques present biomarkers and discover AD or differencing AD and other dementia, which are almost no false positive presenting in result[7]. For example, structural MRI clearly presents the process of AD atrophy from the beginning in the medial-temporal lobe and spreads to the lateral-temporal and parietal cortices [7].

As seen in figure1, structural MRI can highlight where and how atrophy occurs in the hippocampal, left temporal-parietal, posterior cortical, parieto-occipital, frontoparietal hemisphere, and some places around the motor cortex. As shown in Figure 2, there are different PET bio-imagines focused on FDG and TAU. At the same time, non-invasive diagnostic imaging has been shown to improve the accuracy of AD diagnosis[6].

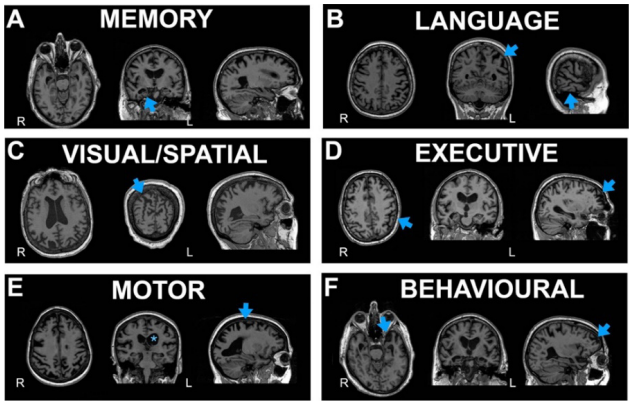

Figure 1. MRI across Alzheimer's disease phenotypes [7].

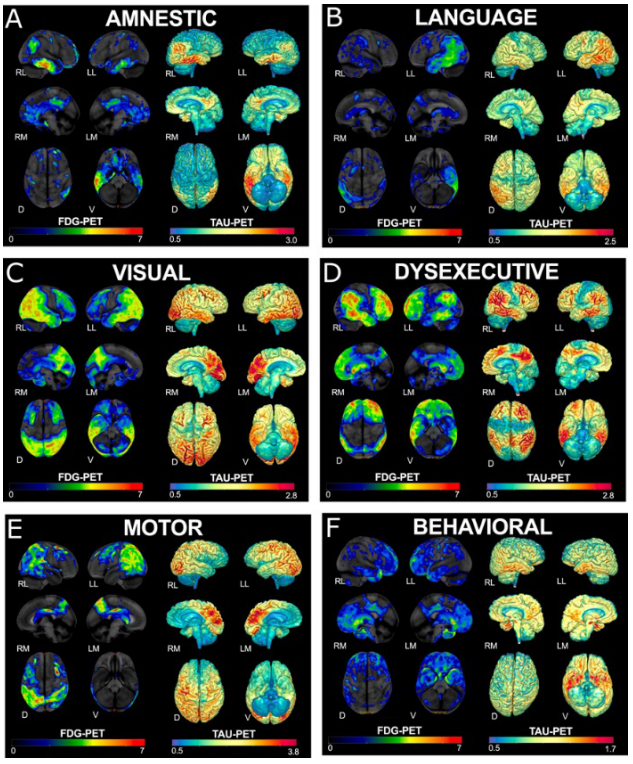

Figure 2: FDG and tau PET across Alzheimer's disease phenotypes [7].

3. Pharmacological significance of tau for diagnosis

Tau is a microtubule-associated protein in the brain that disseminates in the nervous system and stabilizes axonal microtubules[8]. Neurofibrillary tangles of p-tau are a major pathology of AD, so several viable pharmacological treatments have been developed for tau. For example, microtubule-stabilizing agents, tau protein kinase inhibitors, tau aggregation inhibitors, active and passive immunotherapies, and inhibitors of tau acetylation[8]. It is noticeable that tau aggregation inhibitors have the possibility to improve cognitive function, so they can be the most potential pharmacological treatment and need to be excavated. However, what is more promising is the development of clinically effective live vaccines and monoclonal antibodies. In 2016, the active vaccine was in phase I testing, divided into vaccines against phosphorylated tau (AAD-vocal) and non-phosphorylated tau (ACI-35), respectively. Moreover, two anti-tau monoclonal antibodies are also in progress[8].

4. Two types of pharmacological treatment

Cholinesterase inhibitors are a major direction of clinical treatment of AD. According to Zeinab and Rafik, the

physiological process of AD destroys acetylcholine (Ach) cells, which is the main neurotransmitter transmission in the brain to keep thinking. Cholinesterase inhibitor helps to can retard the mechanism that cholinesterase disintegrates acetylcholine which causes Ach reduction in pathological procession of AD. Thus, Ach levels increased to near-normal levels [1]. Donepezil is a representative drug that can achieve this mechanism but is accompanied by certain cholinergic effects[1]. Compared with another cholinesterase inhibitor, tolerance of Rivastigmine will be significantly improved in clinical use. So, in the feasibility of Rivastigmine therapy under the consideration of half-like and dosage. GAL is another cholinesterase inhibitor that needs to be considered in how it is administered to avoid fist-pass effects and target some parts of the body. The above three types of cholinesterase inhibitors are effective drugs for the treatment of mild AD, but there are relatively few side effects. Donepezil is the first choice for mild AD compared to the other two[9].

Noncompetitive N-methyl-D aspartate receptor (NMAR) antagonists are another major clinical drug of AD. Because of the over-activation of NMAR, Calcium influx increases, which promotes call death and causes prominent dysfunction. Thus, NMAR antagonists can retard over activation of NMAR to achieve a reduction of calcium influx[1]. This drug treatment mechanism is mainly used to treat moderate or severe AD. There is a characteristic drug named Memantine, which is very well tolerated.

The effectiveness of combination therapy has not yet been proven and approved[10], so drugs are often prescribed alone. These drugs only relieve symptoms rather than alter the procession of AD or cure it. Also, the desynchrony between pathological processes and clinical symptoms poses great difficulties for diagnosis and drug therapy. So, making a systematic summary and in-depth study of the stages of diagnosis and drug delivery is worthwhile. In terms of drug treatment, a reasonable intake of Vitamin D, Vitamin E, and fish oil combined with regular aerobic exercise are effective ways to prevent AD[6].

5. BACE1 inhibitor drugs

Amyloid β-protein is hydrolyzed by APP, which has a strong neurotoxic effect after cell matrix precipitation and accumulation. Mitochondrial dysfunction caused by Aβ deposition is characteristic of AD[11]. The path mechanism of BACE1 is the main reason for triggering NFT. Specifically, BACE1 splits from two peptides, one called C99, binds to the membrane and is further processed to form Aβ40 and Aβ42. Aβ42 is highly neurotoxic after deposition, which causes NFT of p-tau[12]. Since the concentration of BACE1 is 30% higher in AD patients than in the general population, BACE1 concentration is also used as a biomarker to detect the disease progression[12]. However, the accuracy (77%), sensitivity (73%), and specificity (70%) were low compared to other biomarkers, and the success rate of the experiment was not high[12]. Therefore, the role of BACE1 in detection and analysis needs to be considered, but it may make more effective progress in pharmacological treatment. In 2014, Robert Vassar proposed to evaluate the therapeutic potential of BACE inhibitors to reduce Aβ levels to treat AD[13]. However, there are several difficulties in the research of pharmacological treatment. First, the difficulty in crossing the blood-brain barrier poses a challenge to the method of drug delivery[12]. Second, no relative study presents specific side effects and toxicity. Third, because there is no biology and catalytic mechanism, BACE1 inhibitors may only be effective in some people when used clinically.

6. Conclusion

Difficulties still provide us with the direction of research. For example, maybe we should have some discussion about when to stop drug delivery rather than when to start. In other words, there are some symptomatic patients who need more conservative treatment plans such as vitamin E and acetylcholine supplements. On the other hand, when the direction of disease treatment is difficult to break through, we may wish to turn our attention to the use of biomarkers to be as precise as possible. For example, perhaps we can improve the monition of cortical thickness to determine the Aβ level for tau. All the bioimaging results are quantified to see if the results are more accurate[14]. Regarding pharmacology, health drugs, especially supplemented with vitamin E, vitamin D, and fish oil, are designed for AD patients.

The pathological process of AD can be determined, but what we cannot determine is the pathological process of the patient, and no drugs can be targeted to cure AD. So what needs to be done is prevention and early diagnosis, which is early identification of disease progression by biomarkers for treatment and conservation estimation. The article emphasizes the importance of biomarker studies in diagnosing AD and summarizes the potential drug therapies and the significance of VACE1.

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