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Analysis and comparison of biomarkers for Alzheimer's disease

Xinyi Zhou

Shifang High School, Deyang, Sichuan, 618000, China

2296238305@qq.com

Abstract. Alzheimer's disease (AD), commonly known as dementia, is a neurodegenerative disease that causes memory and cognitive decline. Alzheimer's disease is a neurodegenerative disease that causes memory and cognitive deterioration in patients. 70% of the world's more than 50 million elderly patients suffer from Alzheimer's disease. Currently, scholars around the world mainly classify Alzheimer's disease (AD) patients into seven stages from onset to death. The pathogenesis of Alzheimer's disease (AD) has not yet been clarified by studies on different stages, and the main theories include the A-β amyloid hypothesis and other theories such as abnormal phosphorylation of Tau protein. The A-β amyloid hypothesis proposes that a type of Aβ42 forms a large number of oligomers in the patient's brain due to misfolding and accumulation, which then develop into mature fibres and protofibrils, eventually accumulating into plaques that impede signalling between the patient's nerves and neurons to cause problems in the brain. The Tau protein theory proposes that it is due to over phosphorylation of pTau protein that disrupts the neuronal skeleton and forms neuronal fibre tangles (NFTS) causing impaired axonal transport to affect signalling. fibre tangles (NFTS) causing impaired axonal transport to affect signalling. This review provides an overview of the Aβ amyloid hypothesis and the abnormal phosphorylation of Tau protein hypothesis, and compares their pathogenic mechanisms and proposes ideas to address the different mechanisms. This thesis finds that Alzheimer's disease (AD) can be treated using targeted approaches for different pathogenic mechanisms.

Keywords: Alzheimer's disease, A-β amyloid, Tau protein.

1. Introduction

Alzheimer's disease patients are broadly divided into seven stages from onset to death: latency, subjective decline in consciousness, mild cognitive impairment, mild dementia, moderate-to-severe stage, severe dementia, and end-of-life stage. *The World Alzheimer's Disease Report 2022* published by Alzheimer's Disease International (ADI) states that the number of people with the disease is expected to reach about 80 million in 2030. Alzheimer's disease (AD) has brought a heavy burden and impact on people of different ages and families in today's world, and it is important to find out as soon as possible what are the main pathogenetic principles and the mechanisms that are responsible for its development [1]. A-β amyloid is divided into Aβ42 peptide and Aβ40 peptide, which are deposited in nerve cells and around blood vessels in the brain, causing inflammation/damage to nerve cells and leading to nerve fibre entanglement to block signalling. Tau protein itself is a microtubule-associated protein distributed in the

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axons of CNS neurons, which is usually subject to various modifications, mainly phosphorylation, but when over-phosphorylated, it loses its microtubule-binding function, leading to impaired axonal transport and accelerated neuronal cell death due to the accumulation of Tau aggregates [2]. This review will illustrate the different stages during the onset of AD in patients and will summarise and compare the two pathogenetic theories and present ideas for future treatment options. The research presented in this thesis will provide ideas for future research into AD as well as envisioning possible solutions.

2. Different stages of disease progression in ad patients

Usually, the latency period of Alzheimer's disease is very long, research shows that most of them are 10 to 15 years, and AD patients have to go through seven stages from the onset of the disease to their death. At the beginning of the disease, due to irregular lifestyle or lack of exercise, depression and other anxiety, or even genetic factors, the patient has already entered the latent phase, and amyloid deposition in the brain has already begun, which mainly manifests itself in mild symptoms, similar to occasional forgetfulness...After about 15-20 years the patient's subjective awareness declines, and the patient, as well as those around the patient, will notice that the patient's memory is deteriorating. After another five years or so, the patient enters the stage of mild cognitive impairment, in which the patient shows serious problems of doubt, similar to forgetting to close the door when leaving the house, forgetting to turn off the fire, etc. However, they are usually still able to take care of their own lives, but it is only in their daily lives that they can pose a greater safety hazard. At this stage, hospital tests can already detect positive amyloid, but many drugs that work on amyloid also work best at this stage, such as Adu, a monoclonal antibody drug that works on amyloid to suppress the disease. However, once this stage is missed, amyloid builds up in large quantities in the next stage, and the drug's effect is very limited. After 3-5 years the patient will enter the stage of mild dementia, which usually already affects the patient's daily life, and the disease will progress more and more rapidly. If no intervention is made at this stage, after another 1-2 years, the patient will gradually enter the stage of moderate-to-severe dementia, and people around the patient will notice that the patient is no longer able to take care of himself/herself, which mainly manifests itself in the form of poor eating, answering questions incorrectly, and even recognising relatives wrongly and not being able to remember the date, and so on. After 1-2 years, the patient will enter the stage of severe dementia, the patient's personality may change, may become depressed, and even aggressive, He cannot even take care of basic living habits such as defecation and eating. This time the patient must need to be accompanied by a person to live, otherwise the probability of accidents is very high. Finally, the patients will enter the end stage, they no longer have the fundamental senses, similar to hunger, and excretion needs enema and other methods can be carried out, for the stimulation of the side cannot respond, and even part of the patients cannot walk. Therefore, for AD patients, early detection, early intervention and early medication are very important in the first, second and third stages.

3. Analysis of the doctrine of the pathogenesis of ad

3.1. Aβ amyloid

Beta amyloid is a protein that is inherently present in our brain, and unlike any protein present in food, through misfolding and degradation and removal, many oligomers consisting of protein monomers entangled in the brain are formed, and these chunks of oligomers in turn begin to bind and deposit, and after roughly 20 years protein plaques are formed, and are a currently thought to be an Alzheimer's disease in the world. Alzheimer's disease core pathology. Regarding the formation of amyloid plaques, it can be seen that there are different neurons in the brain that send signals for daily communication, one of which is the amyloid precursor protein APP, and all amyloid precursor proteins in the brain of a normal person are broken down by proteolytic enzymes into small pieces and flushed out of the body through the lymphatic circulation and other pathways after their action, but in the brain of an AD patient, these proteins are incorrectly broken down into pieces of different sizes However, in the brains of AD patients, these proteins are incorrectly broken down into different sized chunks, resulting in larger proteins not

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being able to be degraded, and more and more proteins building up and eventually combining to form large plaques [3].

If amyloid is used as a marker to detect AD there are some challenges, amyloid deposition also starts in small areas, and during this time the patient will experience symptoms that are only occasional forgetfulness, this is the time when even many patients and people close to them will not notice the patient's problem and go to the hospital in time, there is a certain time lag, hospitals are now usually able to detect the amount of amyloid in the brain by a Pet- ct method to detect the amount of amyloid in the brain, but the channels are not much for the general public. Secondly, amyloid itself can be regarded as a substance present in the brain, and it is very difficult to find a commonly used method, for example, through blood sampling. In the case of blood sampling, for example, it is very rare in the blood, so many academics are also researching on and implementing this technique. However, from other aspects, as mentioned earlier, there is actually a time lag of 10-20 years between the deposition of amyloid to a certain amount and the emergence of irreversible symptoms in patients, and using this characteristic, it may be possible to study the relative therapeutic drugs through the amyloid hypothesis, so that it can be used as a therapeutic target for the study of drugs, with a relatively smaller difficulty than that of detecting it by everyday means.

3.2. Tau protein

Tau proteins, mainly classified as TTau and PTau, are microtubule-associated proteins mainly found in brain neurons. Their main role is to contribute to and protect the stability of microtubule proteins, and Tau proteins have a variety of post-translational modifications, of which phosphorylation is the most common [4]. Appropriate phosphorylation can maintain the normal activity of the organism, but excessive phosphorylation will mainly cause PTau protein to lose the ability to bind to microtubules and form neurofibrillary tangles to damage nerve cells. However, the exact role of excessive phosphorylation of Tau proteins in pathological processes is currently unknown, and it is also a possibility that neurofibrillary tangles affect signalling.

Nowadays, it is easier to diagnose AD by means of Tau protein indicators, such as after a brain impact, TTau will be significantly elevated, and combined with amyloid levels, the patient can be diagnosed with AD, so Tau protein has a greater prospect for the detection of Alzheimer's disease. In addition, the level of Tau protein and the decline of cognitive function are actually inversely related, to how much the level increases, and how much the cognitive function decreases, so now Tau protein is more used in diagnosis. Comparatively speaking, Tau protein as a target for drug research will be more difficult, the main difficulty is the over-phosphorylation of Tau protein, but at present, the breakthrough of this technology is more difficult, and due to the relationship between Tau protein and cognitive function, when people through the research of Tau protein drugs for AD patients have passed the stage of the best therapeutic efficacy, so at present the Tau protein is also more used in the diagnosis.

4. Treatment programmes

4.1. Therapeutic options for targeting Aβ amyloid

The central component of the Aβ amyloid hypothesis is the accumulation of amyloid, so if amyloid is to be targeted, the main challenge is to develop a substance that can effectively and rapidly degrade the accumulated amyloid, or to synthesise an agent that can inhibit amyloid synthesis [5-6]. Currently, acetylcholinesterase inhibitors (AChEIs), as inhibitory neurotransmitters, can briefly inhibit the disease but do not act at the root of the amyloid build-up, and other drugs, such as adunumab, can effectively break up amyloid plaques but are highly limited by the duration of treatment, so if patients do not receive these drugs in phases I, II, and III, the effectiveness of the drug is greatly reduced. The effect of the drug will also be greatly reduced. Therefore, up to now, there is no one drug that can completely treat Alzheimer's disease.

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4.2. Therapeutic programmes targeting Tua proteins

To address the Tau protein theory, we need to pay attention to its over-phosphorylation, effectively inhibit and control the degree of its phosphorylation, or work on the repair of nerve cells damaged by over-phosphorylation, using recombinant proteins and other technologies [7]. At present, the world has proposed that a variety of Chinese medicine extracts can be used to combine with over-phosphorylation, similar to berberine, epimedium glycoside, aspalathin, chuanxiongzine, andrographolide, curcumin and so on, all of which are able to inhibit the over-phosphorylation of Tau protein, and in addition, it can also envisage that people can act on repairing damaged neuron cells by synthesising agents to help repair, or implanting proteins to help repair, which are all hypotheses about the Tau protein repair of neuronal cells by Tau proteins, and so far none of the drugs are clinically applicable.

5. Conclusion

This paper focuses on two hypotheses of the pathogenesis of AD and the response options for different pathogenic mechanisms. So far, Alzheimer's disease is still a common problem faced by mankind, and the most urgent task is to find out the main pathology leading to AD, because AD is affected in many aspects, it will be a difficult task to develop drugs to work after determining the pathogenesis, perhaps we can consider multi-targeted therapy to work on different causes of the disease at the same time in view of the nature of AD, and in addition, by using some complementary therapies, such as psychotherapy, can also effectively alleviate patients' pain and promote the treatment to a small extent. In addition, some complementary therapies, such as psychotherapy, can also effectively reduce the pain of patients and promote treatment to a small extent. This paper mainly describes the two major pathogenic mechanisms and does not mention other hypotheses or practical experiments to explore the feasibility of the theory, but in view of the above analysis, scholars in the future can combine the Tua protein and Aβ amyloid to detect AD and Aβ amyloid to study the treatment options for AD.

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