

Challenges in Early Diagnosis and Treatment of Alzheimer's Disease

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Abstract. At present, Alzheimer's disease (AD) has become a hot topic in biology, medicines and other fields. It is a neurodegenerative disorder which is one of the main causes of dementia globally, and population of AD patients is predicted to continue increasing, leading to heavy burden on both health care resource and financial cost. There are numerous new research results considered potentially contribute to new diagnosis or treatment methods of AD annually, but it still lacks a treatment to completely cure this disease, and even though the biomarkers of AD can be detected in the preclinical stage which is more than 10 years early than onset clinical symptoms appear, most of patients are diagnosed after they have cognitive impairments and other symptoms. It still needs to solve challenges on different aspects to find more effective diagnosis methods and treatments. This review briefly summarizes the challenges in early diagnosis and treatment of AD occurring in research or clinical practice in recent years and analysis the reasons and potential study directions of solving these challenges, aiming to give suggestions to help further research.

Keywords: Alzheimer's Disease, early diagnosis, treatment.

1. Introduction

Nowadays, Alzheimer's disease (AD) has become a research highlight in medical and biological fields. AD is a neurodegenerative disorder causing neurocognitive function impairment [1]. About 50 million people globally suffer from dementia [2], and AD is the most important causes of dementia among people over the age of 60 [1]. Around 50-75% of people with dementia are AD patients [1]. In addition, it is predicted that the prevalence of AD will continue to increase all over the world with increased life expectancy and demographic ageing, especially in developing countries [3]. The population of AD patients is expected to triple by 2050, causing an expansive burden including healthcare and hospice support for patients and lost productivity from patients and caregivers [4]. To solve this serious problem, research for early diagnosis and treatment methods of AD is very needed.

AD is a progressive disease with long course, especially the long asymptomatic phase. For individuals aged 70, the total duration of AD is estimated to be 20 years, among which 10 years are the preclinical stage, 4 years are the prodromal stage, and the dementia stage is only 6 years [2]. Both the two most typical pathology of AD, extracellular amyloid beta (A β) plaques and intracellular neurofibrillary tangles (NFTs), occur more than 10 years before the onset of cognitive impairment (A β plaques can be found about 20 years before and NFTs can be found 10-15 years before) [4]. Though AD cannot be completely cured now, there are many drug-based or non-drug methods can reduce the pathology progression [1]. Treatments had at the early stage of AD can have better effect on AD patients than those at later stages, for they can retard the disease process when the brain is not impaired seriously [5]. Early diagnosis is the premise of early taken treatment, thus, research of more efficient diagnosis method become significantly important. However, there is still a lack of more efficient early diagnosis methods of this disease, making new research very urgent. Also, making profound studies of AD treatment is important, as AD still cannot be cured permanently so far, even the medications reducing disease pathology progression is limited [1]. The failure rate of AD drug development is also very high, probably due to complexity of the pathological mechanism [6].

This paper summarizes and analyses challenges in early diagnosis and treatment of AD recently, trying to provide help and suggestion for future research and contribute to solve the problems.

2. Challenges in Early Diagnosis of Alzheimer's Disease

So far, most of the common clinical diagnosis of AD was limited to the stage with symptoms, and the diagnosis of the symptomatic phase still has difficulties. The biological diagnosis methods, which rely on biomarkers, is thought to be promising. But with research furthers, the biological definition of AD and the diagnosis based on biomarkers also meet debate and challenges in clinical practice [7].

Recently, it is recommended AD care should be developed into a more patient-centric, cross-disciplinary model, and the whole diagnosis course of AD can be divided into four steps: detection, assessment/differentiation, diagnosis, and treatment [4]. The treatment step in this classification criteria actually means the following examination after reaching a diagnosis. Thus, the analysis of challenges in diagnosis focuses on the detection, assessment/differentiation and diagnosis steps.

2.1. Challenges in Clinical Detection and Assessment of AD

At the detection step, patients are found having overt clinical symptoms suspected AD like short-term memory loss, cognitive impairment, behavioral impairment and dementia, and their patient data, such as symptoms, patient history (including family history), caregiver perspective, medical and disease history, and lifestyle data (like smoking, alcohol, exercise), is collected and analyzed to estimate possibility of having AD. The assessment/differentiation step includes blood tests, genotyping, neurologic examination, physical examination, structural imaging, and neuropsychological scale assessment (including cognitive, behavioral and functional assessments) [4]. Actually, these examinations and assessments do not directly make a definite diagnosis of AD, but mainly exclude other causes of cognitive impairment, for instance, vitamin B12 deficiency, depression, thyroid disturbance, vascular diseases, and other less common dementias [8].

The first problem is that patients and caregivers like family members may ignore or misunderstand the symptoms and even refuse to seek medical advices. The most important reason of that may be the lack of awareness and understanding of AD. Patients may not notice their memory loss in the early stage and believe their memory is similar to their peers, because symptoms is not very observable and do not affect their daily life heavily at that stage [4]. And many AD patients and their family members who do not know much about this disease possibly think some mild symptoms like mild cognitive and behavioral impairment are simple parts of the normal aging process which do not serious [4]. And stigma also causes resistance to consultation. Another reason preventing some patients from visiting is poor personal economic condition, especially in less-developed regions. Thus, many patients may not tend to visit clinics or hospitals until the symptoms develop to more severe ones like dementia, missing the chance to reduce the disease progression early before their brains suffer irreversible serious damage.

However, even if patients notice their symptoms and seek medical advices actively, the time taken from first visiting a physician to reach a definite AD diagnosis can lasting for several months, which also delay the start of treatment. Research shows that even in some developed countries with relative better health care in five developed countries (France, Germany, Japan, the UK, and the USA) only approximately half of AD patients obtain diagnostic result within 6 months after their first visit [9]. It suggests that there are other challenges in common clinical assessment of AD currently.

One problem is many physicians may also lack an understanding of AD, make it difficult for them to differentiate symptoms caused by aging or AD. A survey in Europe shows that general practitioners and specialists there have difficulty to recognize early symptoms. The proportion of AD diagnosis triggered by physician's suspicion is not high (only 20% in the five developed countries above). In addition, referral rates of patients suspected to be AD were also low (14–23% in the five countries above), which means patients may waste time on physicians who do not specialize in AD rather than be referred to experts to quickly get diagnosis and begin treatment early [9]. That suggests not only enhancing physicians' understanding of AD, but also strengthening linkage between different hospital departments increasing referral to experts for quicker diagnosis may contribute to solve this problem.

And finally, a fundamental problem of the detection and assessment of AD above is that they can only diagnose AD after the symptoms appear, which means at that stage patients' brains have been

impaired. However, as the most typical biomarkers of AD, namely extracellular A β plaques and NFTs, occur more than 10 years before clinical symptoms, the diagnosis should have possibility to be made earlier by detecting biomarkers. And these clinical examinations mainly differentiate other diseases which can also cause similar symptoms, not directly make a definite diagnosis of AD, which may cause misdiagnosis and take longer time to assess. Using biomarkers to diagnose AD may help to solve the problems of common clinical examinations.

2.2. Challenges in definite diagnosis of AD Using Biomarkers

The diagnosis step here means narrow definition of AD diagnosis: to make more definite diagnosis of AD based on detection of typical biomarkers, namely A β and tau [4]. According to the ATN framework which classifies biomarkers of AD into A β (A), phosphorylated tau (T), and neurodegeneration (N), the purely biological definition of AD is the presence of A β and tau, including both asymptomatic and symptomatic stages [10]. It is thought to be promising to use biomarkers for diagnosis of AD, because biomarkers can be detected in asymptomatic stage, much earlier than onset symptoms, providing premise of earlier treatment. However, along with deeper research, dispute about whether purely biological definition of AD relying on only biomarkers should be used in everyday clinical practice appears, and currently biomarkers also have their limitations in diagnosing AD clinically.

2.2.1 Debate of using biomarkers to clinical AD diagnosis

Diagnostic criteria of AD experienced the change from clinical to both clinical and biological and finally to purely biological over the past several years, emphasizing the important role of biomarkers in AD diagnosis increasingly [2]. In 2016, a consensus was proposed by the International Working Group (IWG) and the US National Institute on Aging and the Alzheimer's Association (NIA-AA) that, due to research purposes, the preclinical stage with in-vivo A β and tau positivity which has high risk of progressing to clinical AD is also included in diagnosis result of AD [7]. And in 2018, the NIA-AA diagnostic framework considered the presence of abnormal A β and tau can be also defined as AD even without cognitive symptoms [7].

However, in 2021, IWG suggested that only people who have both biomarkers positivity and specific AD symptoms should be diagnosed as AD, and biomarker-positive individuals without cognitive impairment should be defined as only having risk of progression to AD, due to debate of using biomarkers. Actually, many individuals who are found having AD biomarker positivity will not develop to cognitive impairment in their lifetime. Currently risk of lifetime dementia is only estimated around 5% to 42%. And biomarkers of AD can also be observed in other brain disease such as dementia with Lewy bodies, so it would cause confusion to purely consider biomarkers without pathology to diagnose AD, for physicians do not know whether it should be defined as patients of these disease also have AD or not. Moreover, biomarkers positivity still lacks defined thresholds currently [7].

Because of these problems, the debate about definition of AD and value of diagnosis based on biomarkers is predicted to still continue for a long time. It is also a challenge in diagnosis of AD, for confusion of diagnostic criteria may cause uncertainty of diagnosis. Physicians possibly offer unnecessary treatments to individuals do not have very high risk of progressing to AD and waste medical resources, or miss to take treatment timely on individuals do have high risk. Relationship between biomarkers and pathogenesis of AD requires further study and clarification to solve this challenge.

Nonetheless, it does not mean the detection of biomarkers is not crucial. Observing the presence of in-vivo biomarkers can be decisive evidence of diagnosis as AD for patients with other clinical symptoms and pathology of that, and also remind individuals who do not have cognitive impairment yet to reduce risk factors and prevent progression to AD. Thus, research for more effective and practical methods of detect biomarkers of AD is still urgent.

2.2.2 Problems in existing common methods to detect AD biomarkers

Now imaging and fluid biomarkers are new ways of finding the potential pathology relating to AD, namely A β and tau [4]. For example, the imaging method, amyloid positron emission tomography (PET) scanning, can visualize A β to support the diagnosis of AD [4]. Collection cerebro-spinal fluid (CSF) by lumbar puncture and analysis present biomarkers can be another alternative method [4]. However, these methods have shortcomings making them cannot be used more widely.

The biggest limitation of PET scanning is the high financial cost. Amyloid PET is high-priced and usually not covered by medical insurance, which makes it not used widely, especially in low-income areas [4]. Relatively, CSF measurement has moderate cost, but the invasiveness of lumbar puncture limits its clinical application [7].

Moreover, due to their limitations, these medical examinations of AD biomarkers are not included in routine physical examinations and usually only be used on individuals with symptoms suggesting possibly to be AD [4]. That means these existing methods generally contribute little to bring AD diagnosis forward to the asymptomatic stage for individuals in this stage do not consider about them, though biomarkers can be detected earlier than other symptoms like cognitive impairments. Examinations detecting AD biomarkers with lower cost and less invasiveness which are suitable for widespread use need to be found.

2.2.3 Challenges in other emerging diagnostic tools

Detections of blood-based biomarkers, including plasma protein markers (A β , tau and neurofilament light) and extracellular vesicles (EV) are considered to be promising diagnosis tools of AD, for blood testing can be less expensive and less invasive than PET and CSF examination and is already included in clinical routines globally. Enormous research results have suggested some methods of detecting and analyzing blood-based biomarkers show potential of make accurate AD diagnosis [11, 12]. However, presently, only limited number of blood-based assays are approved and used on clinical diagnosis [4].

The most problem of using blood-based biomarkers to diagnosis AD is currently the accuracy still need to be improved for realizing clinical applications. Some promising detection methods are described to have diagnostic accuracies only about 60%-70% now, which are not high enough for wider clinical application and need to be improved [11]. Some results are only preliminary proved the relevance between the blood levels or ratios of biomarkers and AD at present, requiring further research. And many technologies of separating and analyzing these biomarkers are still staying in the laboratory stage, thus, more researches are needed to transfer theoretical studies and technologies in laboratory to clinical application.

A potential strategy improving the diagnostic accuracy is using panels of blood-based biomarkers. Amount of multivariate blood-based biomarker panels have been proved to be efficient on AD diagnosis [11]. Analysis of multivariate biomarker panels may combine positive thresholds of many different biomarker indexes to assess and classify the disease more accurate, adapting to the complexity of AD pathological mechanism. But researches considering panels of biomarkers can be also more difficult on multivariate control and analysis, still needing further progress.

3. Challenges in Treatment of Alzheimer's Disease

The biggest challenge of treatment of AD must be that there is still no treatment method can cure AD permanently [1]. And treatments reducing the disease process also have boundedness, including limitations of treatment effects and problems in promotion and application of new therapies. In addition, non-drug treatments are also an important part of slowing down the disease process, but there are challenges leading to failure to achieve the best living and nursing conditions.

3.1. Challenges of Drug Treatment

At present, there is no way to completely cure AD but only are drugs brief the symptoms. Many researches of new AD drugs ended up with failed clinical trials, and the reasons of failures include not meeting clinical endpoints, inefficiency of drug and toxicity and side-effects. The two main challenges hindering research of efficient drugs for AD are the unclear pathogeny and the restriction of drug efficacy by blood-brain barrier [1].

There have already been several hypotheses explaining the cause of AD, but the pathogenesis is not very clear currently. It includes various pathways and proteins, and the chronological order of the events in AD course is also less known, thus, the pathogenesis has complexity [1]. In the past AD drugs only targeted on single pathology and the effects cannot cover all of the multiple pathways of the mechanism. It may be the reason why many drugs fail to reach the aim of improving cognition. Thus, multi-targeted therapies are considered to be an emerging strategy to solve the problem of complex pathogeny [6]. But the premise of research for multi-targeted therapies combining several drugs or other treatments is to illustrate the pathogenesis more clearly. It requires both further promotion of the theoretical study and applying theory to drug development and clinical application rapidly.

Another influence factor of failure in clinical trials is late diagnosis causing delayed treatment. In the Phase 3 clinical trials of many anti-A β drugs before, the levels of A β in subjects with mild AD or even in prodromal stage have been reach the threshold causing irreversible neurological damage [1]. If the diagnosis can be made earlier than the irreversible impairment and the treatment can be taken immediately, drugs may show different curative effect on these early-stage patients. The developments of diagnosis and treatment on AD are closely related.

The delivery of active AD drugs across blood-brain barrier is also a big challenge to show the efficiency of drugs. Currently, nano drug delivery systems show the prospect of being vehicles targeting different treatment sites, for they can make drug molecules easy to permeate across blood-brain barrier and improving their bioavailability [1]. But study for clinical application of this kind of technologies still need to go deeper.

3.2. Challenges of Non-drug treatment

Though do not change the underlying biology, non-drug treatments of AD (including cognitive stimulation, music-based therapies and psychological treatment) are considered important due to their effects on maintaining or improving cognitive function and enhancing quality of life for AD patients [13]. Around 85%-90% of AD patients have neuropsychiatric symptoms or problem behaviors such as noncognitive behavioral symptoms and behavioral and psychological symptoms of dementia (BPSD) in the course causing disease progression, lower quality of life and higher costs of care, and treatment of BPSD only on pharmacology not only has less treatment benefit but even sometimes is related to considerable side-effects and risks for morbidity and mortality, suggesting the importance of non-drug treatment in AD management [14].

Studies on well-being or life satisfaction of AD patients are not many, possibly because this field receives attention not for a long time [15]. Timely starting non-drug treatment to assist other therapies and improve patients' quality of life needs the premises that both early detection of AD and sufficient conditions of medicine and care. The awareness of AD and non-drug treatment's importance need to be improved among people. Especially for the undeveloped countries and areas, it still needs to walk a long way to reach both medical nursing level to improve the non-drug management of AD and adequate economic level to bear the costs.

4. Conclusion

The premise of development in application including diagnosis and treatment of AD is ascertaining and illustrating the complex pathogenesis of AD. The complexity of the pathological mechanism suggests multiple target strategy potentially has higher efficiency than only considering single

biomarkers or pathology in both diagnosis and treatment. A promising research direction of early AD diagnosis is detecting panels of blood-based biomarkers to improve the accuracy, while multi-targeted therapies are also considered to be prospective. And earlier diagnosis may contribute to better efficiency of treatment, for in early stage of the course the irreversible neurological impairments do not happen yet. In addition, accelerating transformation from theoretic achievements in laboratory to clinical application is also important.

Awareness of AD should be improved for not only patients and their care-givers but also physicians. Patients and their care-givers need to increase understanding of AD to detect the early symptoms, overcome the stigma, seek medical advice timely and cooperate with treatment. For physicians, understanding of AD also show a lack now, and linkage between different hospital departments should be strengthened to increase referral to experts in AD and make rapid diagnosis for AD patients.

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