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Early detection of Alzheimer's disease by using genetic biomarkers

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Abstract

Alzheimer's disease (AD) patients show gradually lose ability of memory and interpretation, eventually losing the ability to perform the simplest of tasks. Currently, neuroimaging and cerebrospinal fluid biomarkers are more established methods for detecting AD with high accuracy. Multimodal techniques combined with new deep learning methods can improve the quality of assessment and accurately predict the staging of AD patients. Continuously improving diagnostic methods will pave the way for the future development of promising and effective tools that can simply and accurately detect AD and other neurological disorders at an early stage. While cerebrospinal fluid biomarkers Tau (Tau, Aβ, and neuronal damage), structural Magnetic Resonance Imaging, and PET imaging have proven to have good results in the diagnosis of AD. Blood biomarkers offer the advantage of effective monitoring of disease progression. Blood biomarker clinical applications will be more affordable, facilitate clinical accessibility, and allow for efficient population screening by accurately predicting AD at an earlier stage in an individual's life in the future. Alzheimer's disease places an enormous burden on patients, their families and caregivers, as well as on the health and social care system and society as a whole. As life expectancy increases worldwide, the prevalence of Alzheimer's disease is on the rise, and in order to improve the quality of life of older adults, it is urgent to find ways to prevent or delay the onset of the disease and subsequent dementia. While there are currently no drugs on the market that can reverse the initial pathological changes associated with the disease, early diagnosis in the disease course provides time for all involved to make adjustments so that the patient himself can still be actively involved in the treatment process. As a result, many patients without severe symptoms can live for many years with a good quality of life with access to the best treatment and resources.

Keywords: Alzheimer's disease; Memory; Neuroimaging; Biomarker; Structural Magnetic Resonance Imaging; Beta-amyloid

1. Introduction

Alzheimer's disease (AD) is a brain disorder in which the ability to remember and think is slowly destroyed, eventually losing the ability to perform the simplest of tasks. Alzheimer's disease is the most common cause of dementia among older adults [1-6]. The disease is named after Dr. Alois Alzheimer, who in 1906 noticed changes in the brain tissue of a woman who had died of an unusual mental illness. Doctors examined her brain and found many abnormal clumps and tangled bundles of fiber [1].

These brain tangles and plaques are still regarded as some of the primary characteristics of Alzheimer's disease. The loss of connections between the brain's neurons, or nerve cells, is another characteristic. Neurons transmit signals from the brain to the body's muscles and organs as well as between various regions of the brain. Alzheimer's disease is also thought to be caused by a variety of other intricate brain abnormalities [2-6]. The hippocampus and inner ear cortex are two areas of the brain linked to memory that are first affected. Consequently, language, logic, and social behavior-related regions of the cerebral cortex are also impacted. Numerous additional brain regions eventually sustain injury as well. In the process of Alzheimer's disease progression, patients gradually become unable to think normally, memory

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loss, cognitive deterioration, and swallowing and movement difficulties. According to recent statistics, more than 6.5 million people worldwide are living with AD. Alzheimer's disease was most common in people aged 65 years and older, with 2.41 million people aged 75-84 years and 2.31 million aged 85 years and older. Unfortunately, there is currently no established test for Alzheimer's disease [2-6].

Therefore, early diagnosis and intervention are essential to manage symptoms and slow the progression of the disease. If a person with Alzheimer's disease is informed of his condition in the early stages of the disease, he will receive more thorough care and the patient himself will be psychologically prepared for reassessment, resulting in better improvement. More importantly, early diagnosis also allows for earlier intervention rather than uncontrolled progression of the disease, which improves quality of life and significantly reduces the risk of death. Early diagnosis can also help reduce costs and limitations in the healthcare system: a study by the Alzheimer's Association found that diagnosing AD at an early stage could save approximately $7 trillion. In addition, early diagnosis is even more important for patients when treatments are available that target the underlying pathology of AD [2-8].

The commonly studied neuropathological characteristics of AD include tau proteins and synapse loss or dysfunction. In AD patients, synaptic disruption can result in neurodegeneration and cognitive decline. Early AD diagnosis may be aided by defining the mechanism of synaptic disruption in the pathophysiology of AD. Alzheimer's disease can worsen into irreversible dementia in the elderly, but there is yet no proven cure for the condition. Therefore, early detection of AD is critical for the development of novel therapeutic approaches as well as for the prevention of irreparable brain damage [2-8]. The current diagnostic approach to Alzheimer's disease is limited in that it usually consists of observing whether or not the patient is experiencing mental decline, but by the time the patient is experiencing a clearly observable decline in mental ability, he or she has already suffered severe and irreversible brain damage. Develop a new way that can easily and accurately detect Alzheimer's disease before it develops these devastating symptoms is the new target of researchers. Studying biomarkers is considered by experts to be the most promising path forward. AD testing is a lengthy process that combines neurological, psychological testing, imaging, genetic and psychological parameters. Novel biomarker discovery and cost-effective early non-invasive diagnostic methods are extremely necessary to manage the growing number of AD and its treatment. Existing neuroimaging techniques are effective in identifying biochemical features of brain dysfunction [2-8].

A number of putative biomarkers are being investigated to see whether they can indicate early stages of Alzheimer's disease. Such as beta-amyloid and tau levels in cerebrospinal fluid (CSF) and changes in the brain detected by imaging. There are some researchers suggest that these indicators may change at different stages of the disease process. For safety reasons, before biomarkers can be utilized with medical diagnostics, a large number of validation trials must be completed, i.e., multiple studies on a large number of people with different conditions to determine that the biomarker can accurately indicate the state of the disease. In other words, the true relevance of the biomarker to the disease has to be demonstrated through a large number of experiments. It is also important that the method used to determine the biomarker in the laboratory must be stable and reliable with certain standards [9-13].

Good biomarkers can pinpoint the pathology and physiology of a disease. Body fluids such as cerebrospinal fluid, urine, and plasma contain a variety of biomarkers. Multiple cerebrospinal fluid-based biomarkers, such as Aβ and tau, can be used in conjunction with neuroimaging techniques to sensitively diagnose AD. So far, the major cerebrospinal fluid biomarkers phosphorylation tau (p-tau), total tau (t-tau), and Aβ42 have been highlighted as valid biomarkers for the detection of AD. Other biomarkers associated with oxidative stress, urine, blood, and inflammation have also been extensively explored to test their utility in the early detection of AD. Although much is known about biomarkers in body fluids, more efforts are needed to understand how these biomarkers can be used in the diagnosis of Alzheimer's disease. Therefore, monitoring multiple biomarkers simultaneously to improve tracking of disease progression is a path we can consider in the future [9-13].

Biomarkers can be skillfully used as diagnostic tools for early AD diagnosis and associated risk assessment, which will help to guide therapeutic decisions as well as monitor individual treatment/care in clinical practice. Metabolites that change during the progression of disease from mild to severe can be used as biomarkers, and any changes in these molecules help characterize the different stages of disease development. The search for new biomarkers is critical for the early detection of Alzheimer's disease and for preventing death in patients. However, developing biomarkers that can be effectively used for AD detection requires going through many validation processes, such as analysis and clinical validation [9-13]. The ideal AD biomarker should have high detection sensitivity and specificity (able to distinguish AD from other diseases and AD patients from healthy patients). In medicine, the use of biomarkers is becoming a promising approach to studying diseases and finding treatment strategies. Biomarkers can also be used as potential screening tools for disease prevention programs. Biomarkers of neuronal loss, dysfunction, and various protein deposits can be

obtained by cerebrospinal fluid analysis or neuroimaging in both research and clinical settings, and these biomarkers are being widely used to detect AD [12-13].

2. Genetic Biomarkers

Genetic testing is a medical test that determines a person's genetic makeup by analyzing DNA in blood or saliva. Some gene combinations may alter the risk of dementia. Genetic testing is not often used clinically to determine the likelihood of developing Alzheimer's disease or related dementias, but it may be necessary in some special cases [14-19]. Genetic counseling is often provided to patients prior to genetic testing and upon receipt of test results. Genetic counseling includes a discussion of the risks, benefits, and limitations of test results. Among other assessments, genetic testing is used to predict the adverse effects a disease may have on a patient, to help study how to diagnose the disease at an early stage, to determine the course of the disease, and to formulate the most appropriate treatment based on a person's genetic makeup to achieve a good treatment outcome [14-19]. Although most cases of AD are sporadic, in a very small number of cases, a number of genetic factors such as mutant APP, apolipoprotein E (ApoE), progerin 1 (PSEN1), and progerin 2 (PSEN2) cause familial hereditary AD. mutations in these genes lead to structural changes in the γ-secretase enzyme and APP, which can increase the accumulation of Aβ. ApoE is produced by non-neuronal cells to transport lipoproteins in the brain. Various isoforms of the ApoE allele are present in vivo, e.g., ε2, ε3, and ε4. Of these alleles, ε4 is highly correlated with an increased risk of AD, as pureblooded individuals have a higher incidence of AD [14-22]. ApoE proteins are predominantly found in astrocytes of the CNS. Brains with sporadic AD highly express ApoE mRNA [14-22]. A study showed that ApoE ε4 expression was associated with neuropathological and behavioral deficits. The significant effect of this allele was on situational memory decline but not other cognitive declines. Genetic mutations can cause disease, and in the absence of mutations, the risk of disease is mostly determined by common polymorphisms in genes. Common polymorphisms of genes interact with nongenetic risk factors. Recent genome-wide screening methods have identified several additional Alzheimer's susceptibility sites, and more may be found in the future. Despite current difficulties and limitations, genetic analyses have laid the groundwork for understanding the various pathologic mechanisms that lead to neurodegeneration and dementia in AD and other neurodegenerative diseases [14-22].

Genetic tests exist for APOE ε4 and for rare genes associated with EOAD. Traditionally, screening for AD associated genes by targeted sequencing has been more commonly used than whole-exome sequencing because it is less expensive and faster to analyze. The reduction in cost and run time, as well as the use of improved NGS methods, has made whole exome sequencing a more widely used genetic screening tool [14-22]. However, because there is no effective treatment or prevention, routine clinical testing for early diagnosis is not currently recommended for most people with EOAD. In addition, because mutations may vary in penetrance and gene expression, detection of a mutation does not determine disease or age of onset. However, a growing body of research reports the benefits of early disclosure of an Alzheimer's diagnosis in terms of allowing patients to better plan for their future and access good medical care and support services. In fact, for patients with early-onset dementia, when one or more family members with the same early-onset dementia condition are found, doctors will recommend PSEN1 and PSEN2 testing [23-25].

3. Cerebrospinal Fluid Biomarkers

Cerebrospinal fluid is a protective, clear and insulating fluid that surrounds the brain and spinal cord. Cerebrospinal fluid also provides a variety of nutrients and chemicals that play an important role in keeping brain cells in a healthy state. Changes in the levels of these chemicals can be measured by testing the cerebrospinal fluid, which can help detect the state of the nervous system and diagnose problems in the nervous system. Doctors obtain cerebrospinal fluid through a lumbar puncture. In clinical practice, cerebrospinal fluid biomarkers can be used to help diagnose Alzheimer's disease or other types of dementia [14-22]. Cerebrospinal fluid biomarkers are important tools for early detection of neurodegenerative diseases and for assessing the effects of experimental drugs. The three main brain features of Alzheimer's disease (AD) are extracellular amyloid plaques, axonal degeneration, and intra neuronal neurofibrillary tangles, which can be monitored with cerebrospinal fluid (CSF) biomarkers amyloid β-42 (Aβ-42), total tau (T-tau), and phosphorylated tau (P-tau), respectively. They have a high correlation with AD, so they can be used to diagnose AD more accurately. As single center studies and large heterogeneous multi-center studies have shown, they can also be used in the mild cognitive impairment stage of dementia. However, the levels of biomarkers measured by different studies vary widely, as does the diagnostic accuracy of biomarkers. These differences may be the result of preanalysis, during analysis, or production process factors influencing the detection of relevant factors. Preanalysis factors include study participant selection, sample handling, and sample storage [14-25].

4. Beta-amyloid (Aβ)

The main component of amyloid plaques that accumulate with age is Aβ peptide. It is known to accumulate in the cerebral cortex and hippocampus in the early stages of Alzheimer's disease. Because Aβ42 is more hydrophobic and fibrillar, it is the main type of Aβ deposition. These Aβ aggregates can damage synapses, eventually leading to neurodegeneration and dementia [26-27]. It is hypothesized that the accumulation of Aβ42 in the cerebral cortex is the result of excessive production of Aβ42 and/or decreased flow of Aβ42 through the blood-brain barrier into the cerebrospinal fluid. Regardless of the specific mechanism, cerebrospinal fluid levels of Aβ42 are reduced as a result. Reducing baseline cerebrospinal fluid levels may be a potential basis for the diagnosis of AD. Although most of the existing studies on Aβ-peptide in cerebrospinal fluid of AD have focused on Aβ42, the potential of Aβ-40 as a biomarker in many studies should not be underestimated. aβ40 is another component of amyloid plaques, which are found primarily in the walls of blood vessels. The value of the ratio of Aβ42 to Aβ40 as A biomarker for AD is also attracting increasing attention. When it comes to Aβ biomarkers, people usually focus on Aβ42 and Aβ40 [20-27]. However, other Aβ variants, such as Aβ43, are also found in AD patients and tend to aggregate into plaques. Elevated Aβ38 levels have been observed in patients with early-onset/familial AD and in AD-related amyloidosis tests [26-27].

5. Tau

Tau protein is a low molecular weight microtubule associated protein (MAP) discovered in the mid-1970s through the study of the factors required for microtubule formation, mainly distributed in the central nervous system, most of which are found in the axons of neurons, and a few in oligodendrocytes [28-30]. Tau protein induces and promotes the polymerization of microtubule proteins into microtubules, and binds with newly polymerized microtubules to prevent depolymerization, maintains its structural stability, keeps the distance between microtubules, influences the attachment point of protein kinase in neuronal axons, and plays an important role in neuronal plasticity. Tau protein also creates the conditions for the growth and extension of axon by maintaining the stability of microtubule system, which can improve the rate and range of synaptic growth. synapse growth rate and extent [28-30]. In addition, Tau proteins play an important role in promoting oligodendrocyte maturation. When Tau protein becomes highly phosphorylated, abnormally glycosylated, abnormally glycated, and ubiquitinated, Tau protein loses its stabilizing effect on microtubules, and nerve fibers degenerate and lose their function. In the field of neurodegenerative diseases, tau proteins have always been a focus of research. Normal tau proteins bind to microtubules, a component of the cytoskeleton, and help maintain the stability of the cell structure. But when tau proteins are misfolded, they aggregate to form neurofibrillary tangles, and these tangles are one of the hallmark features of Alzheimer's disease. Previous studies have revealed that mutations in the genes that encode tau proteins can lead to neurodegenerative symptoms such as frontotemporal lobe dementia. Tau's regular function is regulated by PTMs like phosphorylation, methylation, and acetylation; however, phosphorylation is disrupted in AD. Proteins that have undergone phosphorylation have higher levels of negative charges, or hydrophilic properties, and electrostatic alterations. These modifications impact protein interactions, signaling pathways, and protein clearance. The binding affinity of tau to microtubules is decreased by phosphorylation of the proline-rich domain's threonine 231 and the microtubule-binding domain's serine 214 and 262 sites [28-30]. In healthy individuals, CSF tau concentrations are typically low. Elevated tau concentrations are seen nearly 15 years before the onset of symptoms Elevated CSF p-tau is specific to AD and remains normal in other neurologic diseases, whereas t-tau is indicative of neuronal strength at a defined point Elevated p-tau and t-tau are directly correlated with a higher risk of AD disease, and can be measured with positron emission tomography (PET) technology Measurement. Measurements of CSF AD biomarkers show significant variation between laboratories, which may be due to factors related to analytical procedures and analytical kits. Standardization of laboratory procedures and efforts by kit vendors to improve kit performance may reduce variability and potentially increase the usefulness of CSF AD biomarkers [28-30].

6. Ng and NfL

Loss of synaptic activity and plasticity are several key aspects of AD pathology. Ng is a postsynaptic C terminal peptid. In dendritic spines in the cortex and hippocampus, Ng controls synaptic activity and maintains plasticity with the help of calmodulin. Synaptic degeneration results in less efficient binding of Ng to calmodulin, which leads to disruption of Ca2+ transport and consequent cognitive decline. Major synaptic degeneration occurs primarily in the middle temporal region. The concentration of Ng is increased in the cortex and hippocampus of AD patients because AD pathology results in the leakage of Ng from dendrites in the CSF [31-33].

Neurofilament is a scaffolding protein that is essential for axon growth. Neurofilaments are found in three distinct subunits called heavy neurofilaments (NFH), light neurofilaments (NfL) and medium neurofilaments (NFM).

Neurofilament biomarkers use a non-invasive approach to provide signals of axonal disability at a low cost and to predict progression markers of mild cognition Its levels are stable and low under normal conditions, but are elevated in the CSF and bloodstream during neural axonal injury. In AD, NfL levels in the CSF are dramatically increased, i.e., 50-fold higher than blood levels. In AD, increased NfH phosphorylation has been detected in perinuclear bodies and proximal axons. In the initial clinical phase of AD, increased cerebrospinal fluid NfL concentrations are associated with cognitive decline and various structural changes in the brain over time [31-33].

Currently, cerebrospinal fluid biomarkers have drawbacks, such as lumbar puncture that may lead to patient discomfort. Blood biomarkers, on the other hand, are considered more promising as an alternative to cerebrospinal fluid biomarkers because they are cost- and time-effective, pose low risk to patients, and can meet the urgent need for clinical testing. The development of effective drugs to treat Alzheimer's disease builds on the development of pre-symptomatic tests for Alzheimer's disease, so there is an urgent need to discover more new biomarkers to help develop pre-symptomatic tests for Alzheimer's disease [31-33]. Alzheimer's disease causes a large number of neurons to be destroyed in patients, thus creating obstacles to the use of drugs to eliminate the condition. There are still no robust biomarkers to detect Alzheimer's disease at the preclinical stage, and disease-modifying therapies like alternative biomarkers need to be explored. Brain imaging methods, which can quantify the rate of disease progression, are currently the most commonly used alternative biomarkers, and results from brain imaging can facilitate the identification of beneficial treatments in the early stages of Alzheimer's disease [31-33].

7. Blood biomarkers

In addition to cerebrospinal fluid biomarkers, biomarkers from other, less invasive sources, such as blood, are also being studied. Extracting blood and then making a sample is less painful and less expensive for patients, giving potential biomarkers in blood an advantage over those in cerebrospinal fluid. Some blood biomarkers also have high accuracy in diagnosis, but further verification is needed. However, collection of cerebrospinal fluid samples from patients has several side effects and contraindications. Blood biomarkers are receiving increased attention and their ability to be used as AD biomarkers is being explored [34-42]. Plasma samples contain tau proteins, Aβ40 and Aβ42. Techniques commonly used to measure these biomarkers in plasma include immunomagnetic reduction (IMR) assay. However, without a highly sensitive test, p-tau protein cannot be detected in the blood. p-tau protein is a substance directly related to neuronal death, and its role as a biomarker in the early diagnosis of AD has been confirmed by relevant studies. Plasma tau protein has been used as a biomarker to evaluate its potential for clinical application [34-42]. Meta-analyses have emphasized the relationship between AD and plasma t-tau. Reduced gray matter density was linked to elevated plasma t-tau levels. However, compared to CSF tau, the pattern of brain shrinkage linked to plasma t-tau has been found to differ. A rise in plasma t-tau concentrations is the cause of both the worsening of MCI and cognitive impairment. According to these findings, plasma t-tau may be employed as a screening or predictive diagnostic for nonspecific cognitive deterioration. Numerous investigations using blood-based p-tau analysis have found higher levels in AD patients as compared to normal controls. Because NfL concentrations have been detected to increase in AD patients compared to normal people, NfL is also used as a blood biomarker for effective detection of AD. A small number of studies using standard immunoassay techniques have also found higher levels of NfL in the plasma of patients with AD. Accurate measurement of brain-specific proteins such as tau and Aβ in blood samples relies on immunoassay techniques. Plasma NfL is associated with cognitive, biochemical, and imaging markers of Alzheimer's disease. All in all, there is growing evidence that plasma NfL may be an important noninvasive diagnostic tool for identifying neurodegenerative degeneration and identifying individuals with cognitive decline and brain atrophy tendencies. Astrocytes contain a cytoskeletal protein called glial fibrillary acidic protein (GFAP), which is a marker of abnormal astrocyte activation and proliferation brought on by neuronal injury (astrocyte proliferation). Given that astrocyte proliferation surrounding Aβ plaques is observed during the prodromal phase of AD, GFAP expression is correlated with the density of Aβ plaques found in the AD brain. In addition, CSF and blood samples from people with AD and other dementias show higher levels of GFAP than healthy controls. For example, one study suggested that older people have normal cognitive level with high Aβ accumulation in the brain had higher plasma GFAP levels, implying that elevated plasma GFAP levels could be used as an early blood biomarker to diagnose people at risk for AD before the onset of clinical symptoms [34-42]. In addition, these findings confirm that the onset of astrocyte damage or activation during the presymptomatic phase of AD is associated with brain Aβ burden. APP physiology and soluble amyloid precursor protein (sAPP) α and β produced by amyloid catabolism are associated with major underlying pathophysiologic events in AD. Previously, few studies have examined whether changes in plasma sAPP-α and sAPP-β concentrations are associated with AD. Given that AD is a slowly developing illness and that it is unknown to what degree the blood-brain barrier is compromised, one challenge in finding blood biomarkers for the disease is this. Blood-brain barrier dysfunction in AD patients has been studied by researchers. This condition causes proteins and other molecules to exchange between CSF and blood. Blood is a complicated fluid with a lot of confounding variables, which is another drawback. Standardized procedures are therefore required to prepare samples and analyze them for research. The

reported concentrations of particular analytes may differ in the absence of standardized assay protocols due to different biological sample dilutions, variations in the antibodies used, and variations in the sensitivity and dependability of the instruments [34-42].

7.1. Limitations

Testing for biomarkers cannot be as accurate as testing directly on tissue during an autopsy. Therefore, when an amyloid PET scan is negative, it cannot be concluded that there is no Aβ in the brain at all, or even that there are no or only sparse neuritic plaques [43-45]. Tau PET has a threshold below which the results will not be displayed, and therefore when testing in vivo, there is no way to know what pathologic tau is present in the brain in the event that the test is inconclusive. The tau PET assay has a threshold below which the results are not displayed. However, neither cerebrospinal fluid P-tau nor tau PET identifies the smallest neurogenic fiber changes detectable on neuropathological examination [43-45]. Similarly, there can be undetectable neuronal atrophy when detected by MRI, which can bias the grasp of the number of neurons and thus result in a misjudgment of the extent of pathology. For each biomarker, there must be an in vivo limit of detection, which applies not only to the biomarkers discussed in this article, but to any biomarker [43-45].

8. Other biomarkers

miRNAs are considered potential biomarkers because of their stability and availability in body fluid. Concentrations of miRNAs are higher in cerebrospinal fluid samples from AD patients compared to Aβ40 or Aβ42, thus suggesting that miRNAs are more sensitive biomarkers for early AD detection [46-48]. Next generation sequencing analyses of small noncoding RNAs in exosomes derived from CSF have revealed a significant relationship between miRNA and PIWI interacting RNAs. One study presents a combined signature of three miRNAs and three piRNAs that are effective in detecting AD and further predicting the transition from MCI to AD; the three aforementioned miRNAs highlighted here are miR-30a, miR-34c, and miR-27a. miR-34c expression in the hippocampus has been reported to be increased in a mouse model with amyloid deposits. In addition, miR-34c expression was reported to be increased in the hippocampus of AD patients. In addition, increased miR-30a expression in AD patients has been associated with stress related neuropsychiatric disorders, whereas miR-27a expression was observed to be decreased in CSF samples from patients with AD dementia, thus emphasizing the role of miRNAs as potential biomarkers for the detection of AD. Although miRNA biomarkers are similarly invasively extracted, these markers are still considered to have more advantages than traditional cerebrospinal fluid biomarkers. Even at low concentrations, diagnosis of AD by miRNA biomarkers has high predictive accuracy and is highly stable in body fluids [46-48]. In addition, targeting genes associated with AD can be achieved by those miRNAs that have high expression in the brain. miR-126-3p, miR-23a-3p, miR-151a-3p, miR-194-5p, and miR-451a have been used for early diagnosis of Alzheimer's disease and have shown good results. Therefore, miRNAs have become effective biomarkers for AD. Several other miRNAs, such as let-7, miR-15a, miR-101 and miR-106b, have also been defined as apps that promote Aβ production. miR-125b-5p is abundant in the brain, down-regulated in cerebrospinal fluid, and is involved in tau phosphorylation by altering tau kinase activity and expression [46-48]. In addition, miR-146a-5p causes neuroinflammation and neuronal degeneration. Elevated concentrations of miR-146a-5p were detected in the hippocampus of AD patients [46-48].

9. Comparison of various biomarkers

Advantages of CSF include high sensitivity, ease of detection, and specificity; usually high concentrations, which can predict small biochemical changes in the brain; and cost-effectiveness. The disadvantages are that the test is time-consuming, the extraction method is invasive and unpleasant for the patient, which can make the test intimidating for the patient and is not conducive to popularization in the population [14-24]. The advantages of blood-based biomarkers are that they are not invasive, are easier to obtain, are more time- and cost-effective, and the process of obtaining samples is simple and easy. The disadvantages are that continuous observations cannot be obtained and more precise and sensitive detection techniques are required; and the concentration of blood markers in blood is low and not suitable for obtaining them, and there are also blood cells present in the blood, which can interfere with the detection process. Other emerging biomarkers such as MicroRNA have the advantage of higher concentrations in the body and high sensitivity and accuracy. Disadvantages are the variety of analytical methods and the need for invasive extraction [14-22].

10. Clinical applications

In order to achieve a more realistic preclinical diagnosis of AD, and to achieve a better therapeutic effect and prognostic response of AD, people are constantly trying to find new biomarkers. As mentioned earlier, the most effective improved treatments are most likely to work in the preclinical stages of Alzheimer's disease; As a result, the focus of drug development has shifted from the dementia treatment phase to the preclinical phase. At this stage, previous treatments are only minimally effective, if at all. Few biomarkers have been included in clinical trials compared to the large number of available biomarkers. Biomarkers used in clinical drug studies have been used as inclusion criteria to diagnose the pathological presence of AD and as a tracker of the biological effects of therapy. Despite some negative results, it is clear that biomarkers are an important tool for clinical trials. The key to a breakthrough will be determining what the best biomarkers are. So we need more longitudinal studies of biomarker trails, linking neuropathology to biomarkers, and discovering new biomarkers that reflect other disease processes downstream from the initial pathology of Alzheimer's disease. Undoubtedly, the most promising cerebrospinal fluid and blood biomarkers, as well as parallel neuroimaging biomarkers, will play a significant role in future clinical trials [1-24].

11. Conclusion

An accurate diagnosis remains a difficult task because there is no single definitive technique that can accurately distinguish the different stages of AD. Currently, neuroimaging and cerebrospinal fluid biomarkers are more established methods for detecting AD with high accuracy. Multimodal techniques combined with new deep learning methods can improve the quality of assessment and accurately predict the staging of AD patients. Continuously improving diagnostic methods will pave the way for the future development of promising and effective tools that can simply and accurately detect AD and other neurological disorders at an early stage. While cerebrospinal fluid biomarkers Tau (Tau, Aβ, and neuronal damage), structural MRI, and PET imaging have proven to have good results in the diagnosis of AD, the use of these biomarkers is hampered by high cost and limited availability. Blood biomarkers offer the advantage of effective monitoring of disease progression. There is no denying that biomarkers based on simple blood tests will benefit research, drug discovery and development, and clinical practice. Future blood biomarker clinical applications will be more affordable, facilitate clinical accessibility, and allow for efficient population screening by accurately predicting AD at an earlier stage in an individual's life. Furthermore, there are a number of other humoral biomarkers with promising futures. For instance, lipids, microRNAs, amino acids, and protein/peptide biomarkers have all been investigated to determine whether they have the potential to be excellent biomarkers; some of these studies have produced encouraging findings. Alzheimer's disease places an enormous burden on patients, their families and caregivers, as well as on the health and social care system and society as a whole. As life expectancy increases worldwide, the prevalence of Alzheimer's disease is on the rise, and in order to improve the quality of life of older adults, it is urgent to find ways to prevent or delay the onset of the disease and subsequent dementia. While there are currently no drugs on the market that can reverse the initial pathological changes associated with the disease, early diagnosis in the disease course provides time for all involved to make adjustments so that the patient himself can still be actively involved in the treatment process. As a result, many patients without severe symptoms can live for many years with a good quality of life with access to the best treatment and resources.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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