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Biomarkers as Indicators for Early Diagnosis of Alzheimer's Disease: An In-Depth Study

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ABSTRACT

Alzheimer's disease affects millions of people worldwide and is the most common form of dementia. The risk of developing Alzheimer's increases with age. This neurodegenerative disease is characterized by the deterioration of memory and cognitive functions. Not only does Alzheimer's affect the mental health of patients, but it also affects their immediate family members and caretakers. The later stages of Alzheimer's disease can change the behavior of a person in various ways. Rather than having to witness a family member change so quickly, people often wish they had known that they had AD earlier. Many studies have been conducted regarding methods to predict the development of Alzheimer's disease; however, nothing has been proven definite. One method that has not been discussed enough is the use of biomarkers. Over the years, multiple biomarkers have had success in predicting other major diseases like heart disease, cancer, and diabetes. They are currently being studied for their use in neurological issues. While analyzing multiple studies, this paper aims to establish the effectiveness of using biomarkers to predict signs of Alzheimer's disease. Ultimately, being able to predict Alzheimer's early on will allow the medical industry to create prevention strategies for the future, along with better treatments.

Introduction

In recent years, the study of neurodegenerative diseases has grown in importance. Caused by the death of nerve cells in the central nervous system, neurodegenerative diseases result in loss of movement and thinking abilities. The most common forms of neurodegenerative diseases include Alzheimer's (AD), Parkinson's, multiple sclerosis, and Huntington's disease. Although there is a lot of research done on the impact of these diseases, little is known about how to detect them early on. Biomarkers such as cerebrospinal fluid and blood plasma have recently been studied in relation to the brain and can possibly indicate signs of brain diseases like AD.

A mixed methods study conducted in Taiwan measured the d-glutamate levels of 133 AD patients. The study found that reduced plasma d-glutamate levels are associated with cognitive issues caused by Alzheimer's disease (Chang et al., 2021). As proven, there was a very strong correlation between the body's plasma levels and Alzheimer's disease. Plasma is known as the liquid component of blood which circulates chemicals and blood cells throughout the body. Proteins in plasma, including amyloid-β (Aβ) and phosphorylated tau (p-tau), are continuously being studied to be considered as biomarkers. Blood plasma is ideal for biomarker investigation due to its easy sampling. However, further studies are required to confirm their accuracy for use as biomarkers.

Of the many proteins in the human body, only a few can truly impact the brain and its functions. A Connecticut-based study showed that genes with the greatest biomarker sustainability score demonstrated low regional variability, high brain abundance, and high brain enrichment. In the study, first and seventh place went to the genes linked to two well-researched potential biomarkers of neurological damage: myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP) (O'Connell et al., 2020). The higher the genes ranked, the more impact they had on the brain, meaning MBP and GFAP could be effective indicators of multiple neurodegenerative diseases.

Compared to other fluids, cerebrospinal fluid (CSF) is in closest proximity to the brain and is more likely to absorb proteins that may be representative of activity particular to the brain. A literature review carried out in Georgia discovered that the cerebrospinal fluid of AD patients had substantially lower amounts of Aβ42 than does the CSF of normal patients (Mitchell, 2009). As shown, the levels of particular proteins in CSF differ significantly between individuals with and without Alzheimer's Disease, further proving their connection.

Studying biomarkers for early detection of neurological diseases is significant as it enables medical providers to recognize symptoms before they become urgent. Physicians can initiate treatment at an early stage by recognizing specific indications associated with these disorders. By analyzing biomarkers, doctors can develop more effective treatments and slow the progression of neurodegenerative diseases.

Methodology

The main goal of this research was to analyze if biomarkers can accurately detect symptoms of neurodegenerative disease beforehand. The research conducted is a literature review based on various primary studies. The qualitative method of analysis was used in this research paper to analyze how strong the correlation is between biomarkers, like CSF and plasma, and the brain. For the data collection, studies measuring protein levels in AD patients were utilized. Then, conclusions were drawn about the correlation between these biomarkers and the brain functions. Further research was carried out regarding the identification of biomarkers in the body and the application of them. Only online resources were used in this research and no physical tools or materials. To avoid research biases, multiple articles were used from around the world and analyzed through many viewpoints.

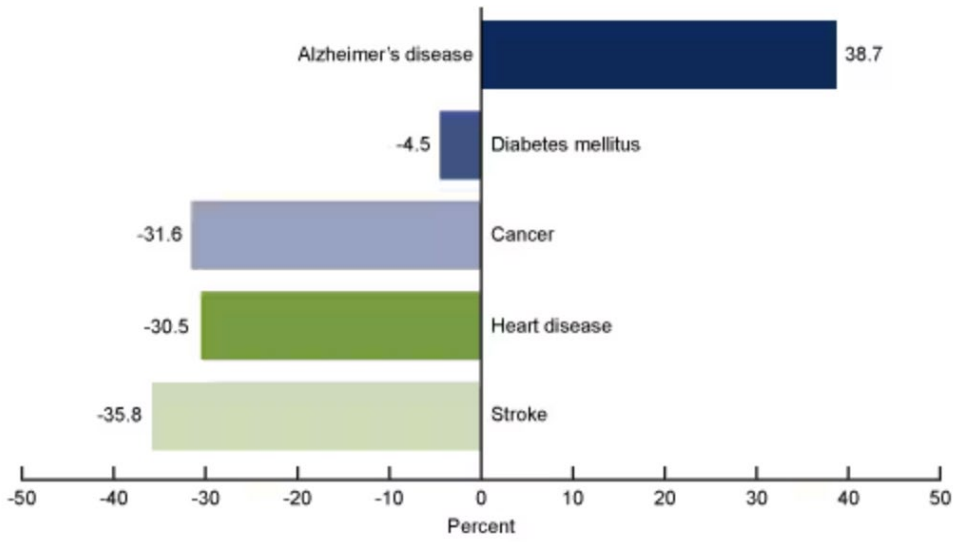

Figure 1. Percent Change in Death Rates Caused by Specific Diseases (United States, 2000 and 2010). Source: CDC (Centers for Disease Control and Prevention), 2013. Description: Above, is a graph showing the percent change in death rates when caused by a specific disease. As seen, Alzheimer's has had the highest increase in the percentage of deaths. It is almost 40% greater than heart disease, which is one of the leading causes of death right now. This underscores the need to conduct more research on Alzheimer's. More research and discoveries can lower the mortality rate along with the number of diagnoses.

Well-Known Causes of Alzheimer's Disease

The specific causes of AD remain mostly unknown. In the development of the disease, nerve cells in the brain stop functioning properly and eventually die. The most common cause of this is a mix of various risk factors. Some of those risk factors include age, environment, and genetics. Psychosocial factors may also influence the clinical pathogenesis of AD (Povova et al., 2012). Alzheimer's can be influenced by all of them, but there is no 100% guaranteed possibility that you will receive it as a result of one of these factors.

Age is the most common risk factor for Alzheimer's disease. The age factor is usually the first thing that comes to mind when someone is asked about AD. According to the Alzheimer's Association, "Most individuals with the disease are 65 and older. After age 65, the risk of Alzheimer's doubles every five years. After age 85, the risk reaches nearly one-third"(Alzheimer's Association). This is because as people age, the more likely they are to develop AD. As humans grow older, certain parts of the brain can shrink and potentially cause harm to some of the nerve cells. The development or progression of damage to the nerve cells is what causes the dementia associated with Alzheimer's.

Another risk factor for AD is the environmental aspects of one's lifestyle. Some of these environmental factors include encounters with chemicals, inefficient sleep, and social stress. Many people often overlook these factors as they seem out of touch with the brain. Studies show that heavy metals like aluminum and lead can enhance amyloid β (Aβ) peptide, causing neurofibrillary tangle formation and neuronal cell death (Rahman et al., 2020). Additionally, a cross-sectional study involving 6000 participants from China, identified a connection between environmental tobacco smoke and dementia risk (Chen et al., 2013). It's often not realized that simple things in one's lifestyle can severely affect one's brain. Sometimes just mere exposure to certain things can trigger not only AD, but also other health issues. Overall, there is proof that geographical variation plays a role in the prevalence of dementia and creates a higher risk of AD in rural areas (Russ et al., 2012).

The least prevalent cause of AD is genetics. Having a family member that has AD might increase the risk of getting it, but no studies have proven its definite identification. Early-onset AD in genetic cases is caused by mutations in the presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes, which encode the amyloid precursor protein (APP). Approximately 1% of instances of AD are caused by mutations in these genes (Vilatela et al., 2012). There aren't many genetic proteins that can truly cause Alzheimer's, but they can increase the risk of developing it. One percent is extremely small, therefore showing how rare these genetic mutations are. But it should be kept in mind that genetics also interacts with age, lifestyle, and environment. Research is still being done to better understand these connections and provide treatment and preventative plans.

Common Symptoms of Alzheimer's Disease

The long-lasting effects of Alzheimer's disease are drastic. The most common symptoms are memory loss, language issues, and disorientation. These effects tend to be symptoms of early-on development. In the later stages, though, the symptoms can get much worse. Psychological symptoms can arise causing hallucinations, aggressive behaviors, and delusions. In a study of 315 Alzheimer's patients, 75 of them had one or more episodes of physical aggression during 52 weeks of observation (Gilley et al., 2015). In addition to aggression, mood swings, despair, or anxiety can result from an inability to regulate emotions. Not only can these emotions be hard to process for the patient themselves but also for the family members due to the distance created by the change in behavior.

One of the hardest symptoms to adjust to is depression caused by AD. Depression affects about 50% of AD patients (Lyketsos & Olin, 2022). Depression can be a serious issue with AD patients as it can put harmful thoughts in their head. It can often spur psychotic urges like mentioned above. The more serious the depression gets, the more life-threatening it can be. Unfortunately, there is no treatment for this kind of depression because antidepressants and therapies can't predict its complex nature. This underscores the need for more research on the mental health of Alzheimer's patients and how they can cope with their emotions.

Social isolation is also one of the big effects of AD that show up in the later stages. Loneliness can be caused by loss of cognitive functions, where higher levels of cognitive impairment increase loneliness (Burholt et al., 2017). As Alzheimer's develops, more distance is created. This causes patients to not speak their minds or show any interest in interacting with others. Family members and caregivers will find it difficult to connect with the patient, leading to a sense of helplessness. This is the main reason why we see a rise in the number of caregivers who struggle with depression. However, there are strategies to help alleviate social isolation like therapy apps, care centers, and community engagement activities.

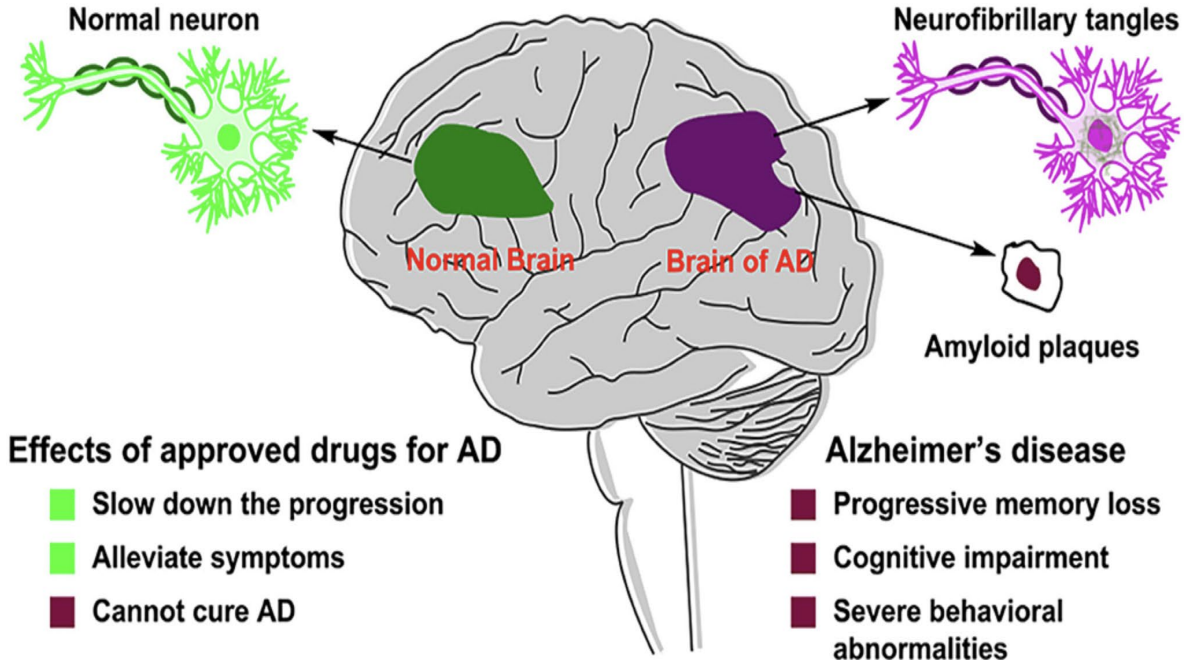

Figure 2. Normal Brain vs. AD Brain. Source: Yao et al., 2022**.** Description: There are major differences between a normal brain and the brain of a person with Alzheimer's Disease. AD brains are known to have buildup of amyloid plaques because of abnormalities. These amyloid plaques eventually cause neurofibrillary tangles. In return, neurofibrillary tangles cause neurons to die in the long run. A normal brain, on the other hand, will have no buildup and be clear of any tangles. As shown, Alzheimer's brain has severe memory loss and impairment in cognitive abilities, indicating less thinking skills. After years of studies, there is still no cure for Alzheimer's. However, certain medications can help slow down the development of the disease and lessen symptoms.

Current Treatments

There is currently no cure for Alzheimer's. However, there are treatments that can help slow down the progression of the disease. When considering drug treatments, medications like donepezil and galantamine are most frequently prescribed (Briggs et al., 2016). They work by increasing levels of acetylcholine, a neurotransmitter important for memory and learning. In addition, serotonin reuptake inhibitors like fluoxetine and sertraline help to treat depression of AD dementia (Zhang et al., 2023). Monoclonal antibodies (mAbs) that target amyloid-β (Aβ) are undergoing phase III studies, as there is evidence supporting their biological target's involvement in people with AD (Perneczky et al., 2023). Other treatments like anti-amyloid therapy and secretase enzymes are currently still in clinical trials to determine if they help with AD. But more research is required on them.

Apart from this, recent studies have shown that brain stimulation from an early age is beneficial for brain health as you grow up. Brain stimulating activities from childhood like puzzles and card games can decrease the risk

of developing neurodegenerative diseases like AD later in life. This is due to the fact that these activities engage the brain and build up its logical reasoning skills. Not only is this good for the brain but it can also help with the mental health of a child. Parents can incorporate these activities into their children's lives if they want to start AD prevention early on.

A study also found that individuals who have greater reserve, measured by levels of education or complexity of occupation independent of education, are likely to show faster rate of cognitive decline after their reserve is depleted to the point of clinical expression of AD (Andel et al., 2006). People who have gone through more rigorous and stressful jobs are less likely to develop AD. But cutting these activities off at an early age can just exacerbate cognitive impairment. This further proves the health benefits of actively engaging your brain, even at older ages. An active brain can make all the difference. This can also be considered as a preventative measure.

The Role of Biomarkers

Biomarkers are essentially measurable indicators of change in the body. They can indicate any abnormal signs about the health of a person or the state of a disease they might have. Studies have shown that biomarkers may be able to predict diseases before the symptoms get severe. Biomarkers have been a big part of the neuroscience field as the cases of neurodegenerative diseases are rapidly growing. Cerebrospinal fluid, along with neuroimaging and blood plasma have been seen to positively correlate with the brain and show the development of brain diseases like Alzheimer's and Parkinson's. "Neuroimaging has become a standard tool in the clinical work up of individuals suspected of having a neurodegenerative disease. The use of various magnetic resonance imaging (MRI) techniques and the development of novel PET ligands have led to the ability to understand these diseases in vivo like never before" (Young et al., 2020).

For a biomarker to be considered beneficial, it must either offer clinically meaningful information that is not already accessible or deliver the same information at a lower cost (Selleck et al., 2016). Lower costs will eventually help out the medical industry a lot as they currently spend billions of dollars every year on neuroscience research. If biomarkers improve their accuracy, we can ensure fewer misdiagnoses and lessen the severity of certain side effects. We can also reduce the need to use invasive procedures for data like biopsies and transplantations.

Cerebrospinal Fluid Biomarker (CSF)

Cerebrospinal fluid is known as the white liquid found surrounding the brain and spinal cord. Its functions are vital for the body's regulation processes. Its role in the body is to protect the brain from sudden shocks, maintain homeostasis, and remove waste products. It transports essential fluids like glucose and sodium ions throughout the body, to meet its energy needs. Because it is located very close to the brain, many of the proteins in the brain absorb into the cerebrospinal fluid, making it a channel for nutrients.

One significant factor of Alzheimer's Disease is a peptide known as β-Amyloid (Aβ). Aβ peptides are known to have roles in synaptic function and plasticity, potentially influencing learning and memory. In patients with Alzheimer's disease, Aβ peptides form insoluble plaques in the brain. The peptide's deposition in plaques, also known as "amyloid sinks," is believed to be the main cause of the decline in CSF-Aβ42 levels observed in AD. The observation is supported by the correlation between low CSF-Aβ42 levels and high plaque burden as determined by PIB imaging, but further evidence is needed to confirm it (Anoop et al., 2010).

Another important CSF biomarker is a protein called tau. The majority of tau proteins are located in neurons, where they attach to and maintain microtubules. Specifically in AD, tau protein becomes hyperphosphorylated and eventually detached from microtubules. In neurons, hyperphosphorylated tau proteins clump together to create unstable formations known as neurofibrillary tangles. The build-up of these tangles is linked to cognitive impairment. Because of the cognitive disruption, tau protein can be released into the cerebrospinal fluid, meaning higher levels of it

in the CSF can be correlated to the neurodegeneration in AD (Anoop et al., 2010). Cerebrospinal fluid is an effective indicator of AD, but it is a challenge when testing because of the difficulty to obtain large amounts of it.

Blood Plasma Biomarkers

When compared with CSF, blood samples are much easier to obtain. They can be collected in large amounts and be stored for a longer amount of time. Just like CSF, though, proteins in the blood like Aβ and tau can be tested for determining AD. Patients with Alzheimer's disease often have increased levels of tau in the blood, which may be related to AD progression. A study involving 103 AD dementia patients found that plasma P-tau181 values in the body enhanced the clinical evaluation of AD dementia patients and predicts AD with high accuracy (Simrén et al., 2021). The proof of high accuracy shows that there is a strong correlation between AD and the protein in the blood like tau, which can be used for diagnosis.

In addition to tau and Aβ, another protein in blood plasma called Apolipoprotein E (ApoE) can also be a factor for Alzheimer's Diseases. A meta-analysis study found that lower peripheral blood ApoE levels are significantly associated with AD and may be an important risk factor (Wang et al., 2014). The ApoE protein has 3 different alleles including ApoE2, ApoE3, ApoE4. The ApoE4 allele is the most important genetic risk factor for AD. A person with two copies of this allele is more at risk for AD when compared to a person who only has one copy of the allele. The ApoE protein is also associated with higher levels of amyloid-beta plaques in the brain, which is a major risk factor for Alzheimer's that was discussed earlier.

Application of Biomarkers for the Future

Although collection of some biomarkers may be difficult, being able to effectively use them will be highly beneficial. Two methods that doctors can use to collect data on biomarkers are neuroimaging and ELISA (Enzyme-linked immunosorbent assay). When considering neuroimaging techniques, PET and MRI scans can be very insightful and effective. "Magnetic resonance imaging is one of the most widely used neuroimaging techniques for the diagnosis of neurodegenerative diseases" (Shimizu et al., 2018). MRI's provide medical providers with detailed images showing the brain structures. These pictures portray changes in certain brain regions which may indicate the sign of a biomarker. Apart from MRI's, PET scans can also pick up levels of Aβ in the brain's fluid, which was one of the biomarkers discussed previously. Quantitative PET studies that use Aβ tracers have shown an increase in retention between Alzheimer's Disease and elderly controls (Ashton et al., 2018).

As mentioned above, ELISA (Enzyme-linked immunosorbent assay) can also be used for biomarker measuring. Its ability to pick up on specific details is why it's regularly used. ELISA can accurately measure certain proteins linked to Alzheimer's. The first step of the process is a microplate covered with antibodies for a target antigen. Then, another antibody connected to an enzyme is introduced. This will end up binding to the antigen. Finally, a substrate will be added causing the color to change if there is an enzyme present. Then, conclusions can be drawn based on the color's hue and intensity. Combining techniques like PET, MRI, and ELISA, in the future, will help better our understanding of the brain and could be the fastest way to diagnose Alzheimer's.

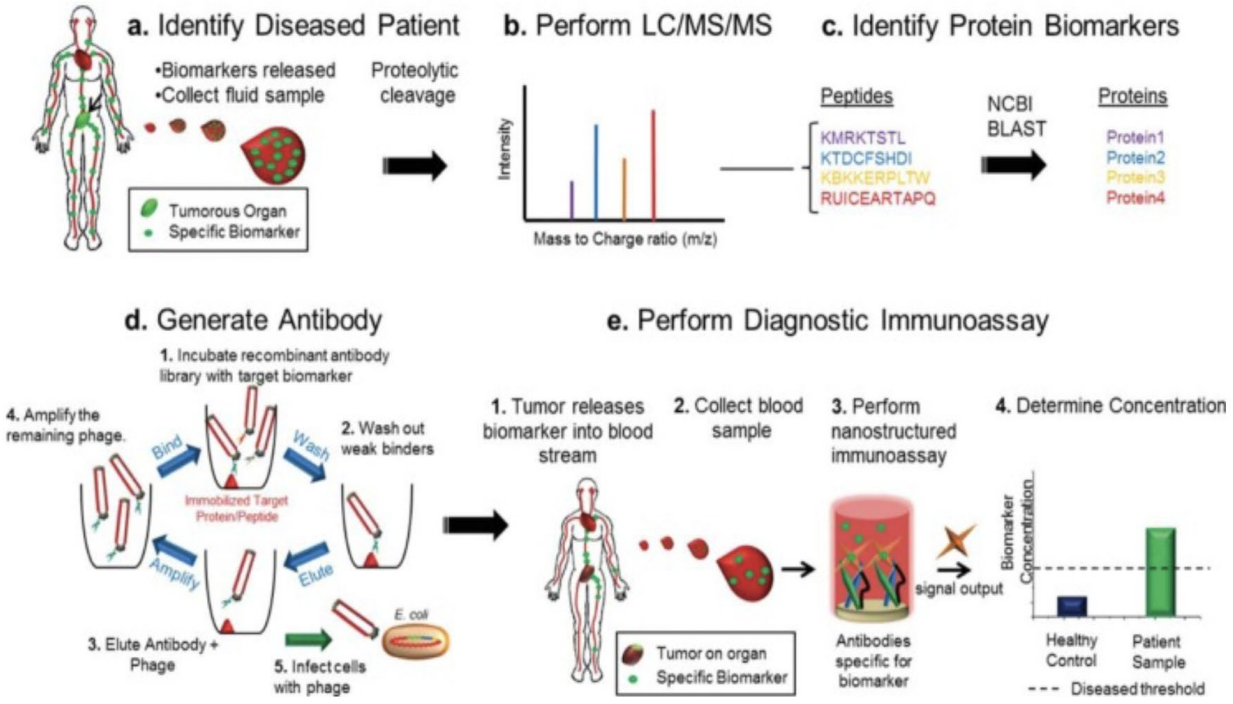

Figure 3. Biomarker Discovery to Diagnosis. Source: Kierny et al., 2012**.** Description: Biomarker discovery to diagnoses is a complicated process. Not only is it a rigorous process, but also a time taking one. The photo above details the step-by-step method. Step a: The body responds to a certain disease by altering levels of proteins fluids in the body. The difference in the levels is what is determined as the biomarker. Then samples of the biomarker are collected. As shown above, the green circles represent the released biomarker. Step b: The biomarkers are then analyzed using the process of mass spectrometry. Step c: The proteins will be identified using amino acids through some sort of national database. Step d: The protein is then incubated with the target biomarker to create antibodies. The strongest antibodies are kept while the weak ones are destroyed. Step e: The proteins, in the form of serum, will be run through immunoassay where it can be truly identified as a biomarker. Once all is confirmed and official, the biomarker can be used. This method will provide the steps for application of biomarkers when encountering symptoms of new diseases.

Results

As proven by this study, biomarkers including proteins in cerebrospinal fluid and blood plasma have a strong enough correlation with signs of Alzheimer's Disease, to be able to accurately predict it. Analyzing data sets from various studies further proved the positive trend between biomarker and AD. The major markers discussed specifically are the increased levels of tau and decreased levels of Aβ in the body's fluids. Tau proteins form neurofibrillary tangles while Aβ forms plaques in the brain. Both proteins are closely related to cognitive impairment primarily associated with Alzheimer's disease and can foretell the symptoms.

The ability to gather stats from Alzheimer's patients is what makes these biomarkers the most ideal for implementation. Even though the collection of a few of these biomarkers is difficult, the application of them in the field of neurology will eventually show promising results. Advances in studies regarding biomarkers will lead to more widespread implementation in clinical practices, which will enhance our ability to treat Alzheimer's disease.

Conclusion

In conclusion, the results prove that biomarkers are in fact able to accurately predict signs of Alzheimer's disease early on. As more studies are conducted in the future, biomarkers will be able to predict Alzheimer's with 100% certainty.

Although there is no cure for Alzheimer's disease right now, biomarkers will allow medical providers to eventually come up with more effective treatments and symptom alleviation strategies. Knowing if a person will have Alzheimer's can help families plan their future and help them make lifestyle changes for a better quality of life. Not only will biomarkers help study neurodegenerative diseases, but they can also help medical providers solve other major diseases within the cardiovascular, digestive, and nervous systems. Overall, biomarkers will allow for a more advanced and prepared medical industry.

Limitations

This research essentially aims to examine the signs of Alzheimer's disease and the extent to which biomarkers can help with the diagnosis of it. As a secondary literature review, various articles and studies were analyzed in order to draw a strong connection between certain biomarkers and the symptoms of AD. Multiple data sets were reviewed to come to a conclusion. Additionally, this study touches on the symptoms of AD and how early diagnoses can help families and patients have better treatment plans. The application of biomarkers in the future was also discussed as results showed that there was a correlation between the biomarkers studied and AD. This research expressed how biomarkers will be beneficial in predicting AD, however, they might not always be a 100% correct. In addition to this, the depression and symptoms caused by Alzheimer's and its diagnosis cannot be completely avoided. Alzheimer's disease cannot be guaranteed by any factor as it is a disease that can be very unpredictable. Overall, this research focuses on the beneficial effects of biomarkers in neurology and their future use.

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