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Early Testing of Alzheimer's using Biomarkers

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ABSTRACT

This paper covers the biomarkers that can be used to test for and diagnose Alzheimer's Disease. This is important due to the large number of people globally who are suffering from this disease. Two types of biomarker origins were explored here: blood and cerebrospinal fluid. Currently, the standard for testing Alzheimer's biomarkers is through the use of cerebrospinal fluid collection. These are the biomarkers that have been thoroughly tested and accepted as accurate and reliable, such as Aβ (1-42) and Tau-related proteins. There are also possible biomarkers found in blood. These include Aβ-related proteins, Tau-related enzymes, as well as inflammatory markers. It has been concluded that the most reliable source of biomarker testing is cerebrospinal fluid. However, there have been significant advancements in studies showing that the use of blood may one day become a very real possibility for routine testing. Until then, it is best to keep a healthy lifestyle that will aid in the prevention of this disease.

Introduction

Alzheimer's is a devastating disease, and it is described as so not only because it renders the patient completely unable to take care of themselves, but it takes a great toll on their loved ones. Furthermore, this is an irreversible disease with no known cure. It has been estimated that 44 million people worldwide were living with dementia in 2013, and this number is predicted to double every 20 years (Sindi et al., 2015). Keeping this in mind, one of the main benefits to an Alzheimer's patient is time. If they had time before the disease affected them, they could use it to get their affairs in order, spend quality time with their loved ones, and communicate how they would prefer to be taken care of once the disease sets in.

Early testing of Alzheimer's Disease can be extremely beneficial in preparing patients for the future. Biomarkers from cerebrospinal fluid and blood can be used to test for Alzheimer's in early age. Previous research has been done extensively on the biomarkers found in cerebrospinal fluid, and this fluid is considered to be the main path taken to test for Alzheimer's biomarkers. However, because the collection of spinal fluid is inconvenient and difficult, another bodily fluid must be used for this testing. Limited research has been done on the use of blood, as it is a relatively new discovery and not as reliable as CSF samples. Both routes of testing will be explored.

Biomarkers

Biomarkers can be defined as medical signs that can be measured accurately and used to determine a specific trait about a patient's health. (Strimbu & Tavel, 2010) It is important to understand what a biomarker is as it is vital in the diagnosis of many diseases. Some simple examples of biomarkers include blood pressure, pulse, and cholesterol (Strimbu & Tavel, 2010). However, most biomarkers are far more complicated in nature, and in turn, more complicated to collect. Biomarkers play an important role in aiding the diagnosis of many degenerative diseases.

Alzheimer's Disease

Alzheimer's Disease is a serious neurological disorder that is most commonly characterized by memory loss. Cognitive decline is also a major characteristic of this disease. Often, Alzheimer's patients will lose the ability to take care of themselves, perform simple tasks, and remember vital information, such as their own name. Diagnosis of this disease requires two things, consisting of clinical assessment and verification of the disease pathology, known as plaques and tangles (Humpel, 2010). The latter is performed post-mortem. The majority of AD cases are sporadic, and few have a genetic disposition (Humpel, 2010). This means that most cases of Alzheimer's occur at random, with a risk age above sixty, and that few cases occur from one's genetic makeup and the passing down of genes from parents to child. The clinical assessment of Alzheimer's usually consists of the collection of biomarkers to ensure proper and accurate diagnosis of the disease. Majority of said biomarkers are found in the cerebrospinal fluid, however current studies show that advances in the use of blood are being made (Humpel, 2010).

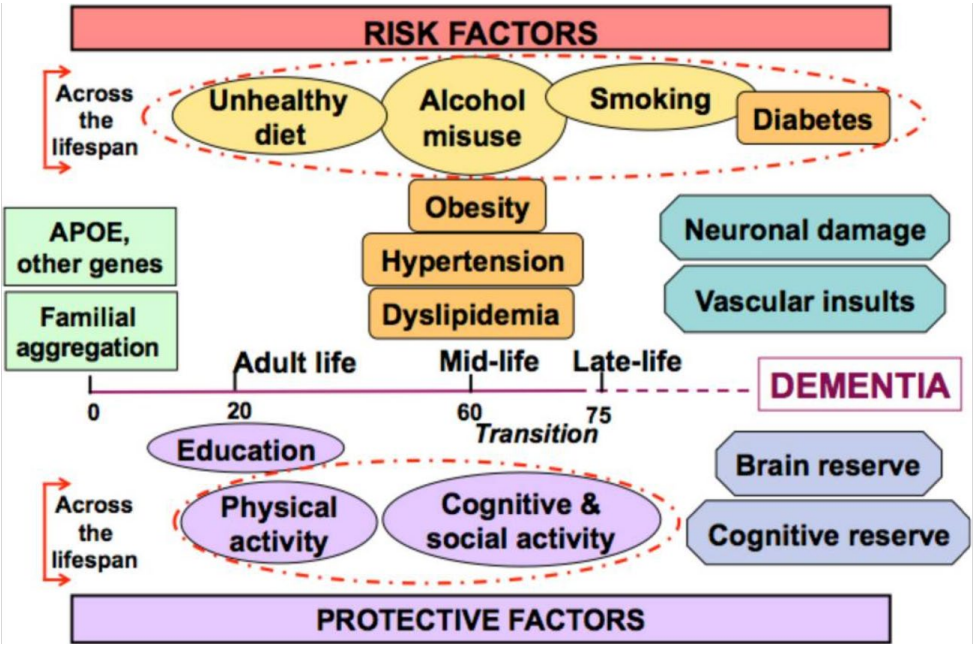

Fig. 1: The most common risk factors for Alzheimer's Disease as well as Dementia (Sindi et al., 2015)

Cerebrospinal Fluid Biomarkers

Aβ (1–42)

Alzheimer's Disease is confirmed by the plaques and tangles found in the brain post-mortem. These plaques are made from depositions of the amyloid β 1-42. Aβ 1-42 is a protein peptide consisting of 42 amino acids (Humpel, 2010). Under certain bodily conditions, such as excess metals or acidosis, this protein can aggregate in the brain, causing a buildup known as a plaque. Using this reasoning, it has been determined that the levels of this amyloid in the cerebrospinal fluid can be used to determine the presence of plaques in the brain. This is due to the fact that plaque buildup in the brain causes less amyloid β to flow down to the cerebrospinal fluid. Analysis of Aβ (1–42) found in cerebrospinal fluid shows a highly significant reduction in Alzheimer's patients compared to controls (Humpel, 2010). As shown below, reduced levels of Aβ 1-42 correlate with Alzheimer's disease.

Biomarker	Controls (pg/ml)	AD (pg/ml)
Aβ(1–42)	794±20	<500

Fig. 2: Reduced levels of Aβ(1–42) in the cerebrospinal fluid are most likely caused by plaque buildup in the brain, causing reduced clearance from the brain down to the spinal fluid (Humpel, 2010)

Total Tau

Another significant biomarker used to test for Alzheimer's is the protein Tau. It is a protein that is associated in the microtubules and found in neurons. In healthy controls, the levels of Total Tau in cerebrospinal fluid increase with age. However, Total Tau levels are significantly enhanced in Alzheimer's patients with a minimum of 600 pg/ml past 70 years of age (Humpel, 2010).

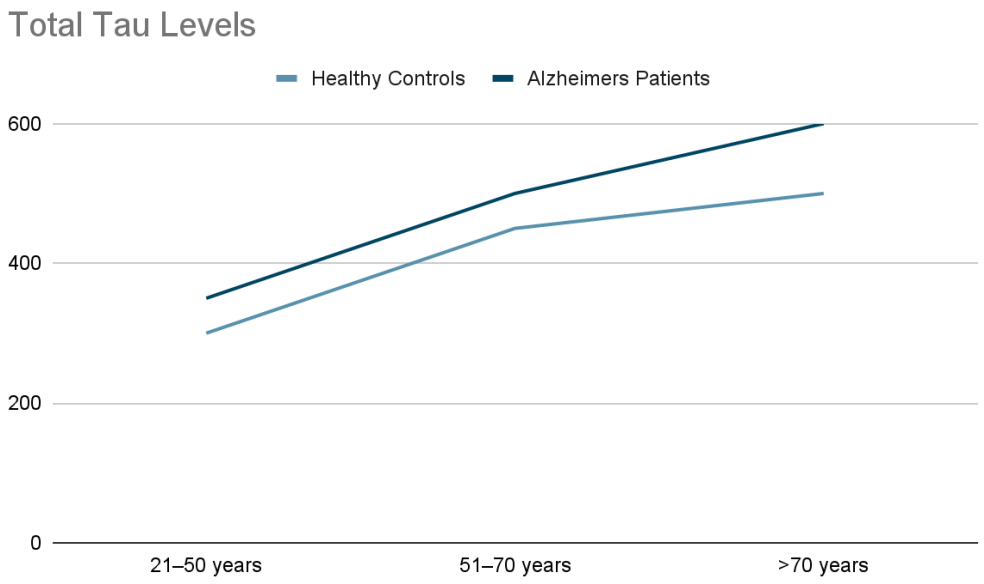

Fig. 3: As shown and explained above, the levels of Total Tau are significantly elevated in Alzheimer's patients (Humpel, 2010).

Phosphorylated Tau

The last cerebrospinal fluid biomarker used to determine the presence of Alzheimer's Disease is known as Phosphorylated Tau, and it is slightly similar to the Total Tau protein covered earlier, as the levels of phospho-tau-181 are increased in Alzheimer's patients. This biomarker is specific to Alzheimer's, and is not widely used for the testing of other diseases, as these levels are elevated in about two thirds of probable Alzheimer's patients, as well as half of possible Alzheimer's patients (Sjögren et al. , 2001). However, in other similarly tested diseases, such as FTD, SAE, and PD, these levels are normal. Furthermore, the collection and analysis of other phosphorylated taus, such as phospho-tau-231, can be used to significantly improve the chance of early diagnosis, as well as differentiate between other diseases (Humpel, 2010).

Blood Biomarkers

Currently, the diagnosis of Alzheimer's Disease through the use of biomarkers is done through the cerebrospinal fluid of the body. However, the lumbar puncture and collection of the specimen is an invasive process, which is not done easily, especially for the patient. In addition to this, the follow up of this process is difficult as well, as it needs to be done over several years, and oftentimes the patient will require thorough assistance for this process. Therefore, the need to find an alternative testing option is prevalent. Other easily collectable body fluids include saliva and urine, however the next best option for biomarker testing is blood, as it is the "gold standard" (Humpel, 2010). The process of actually using blood is still ongoing, but the search has started where progress has already been made: with the accepted cerebrospinal fluid biomarkers. As mentioned above, these include amyloid β and protein tau-related markers. However, further factors such as inflammation, cerebrovascular dysfunctions, and protein/enzyme aging must be considered (Humpel, 2010). The use of blood biomarkers is an ongoing process which requires further research and testing before it is implemented for regular use.

Aβ-related Proteins

When testing for Aβ-related proteins in the blood, there are many different results. Blood plasma levels are increased in Alzheimer's that comes from genetic disposition; however these results are inconsistent in the sporadic cases (Humpel, 2010). High plasma Aβ (1-42) levels have been shown to be a risk factor for developing Alzheimer's disease, but this is only to be used as a tool for early diagnosis. Furthermore, studies continue to emphasize the inconsistency of test results, with plasma Aβ levels showing as increased, reduced, as well as unchanged in Alzheimer's patients when compared to healthy controls (Humpel, 2010). This is most likely due to the fact that Aβ concentration in blood is low and the measurements were affected by matrix effects (Milà-Alomà et al., 2019). However, recent studies using ultrasensitive assays have shown that Aβ(1-42), Aβ(1-42)/Aβ(1-40) ratio, or both show a difference between AD and controls (Milà-Alomà et al., 2019). The magnitude of difference in blood, however, is much smaller than the difference compared to cerebrospinal fluid, making spinal fluid a better option when it comes to accuracy of results. The Aβ(1-42)/Aβ(1-40) ratio, as stated above, has become an extremely helpful discovery when it comes to the use of blood in testing. The Aβ(1-42)/Aβ(1-40) ratio appears to be a better predictor of amyloid positivity, and performs better at distinguishing Alzheimer's from other dementias than Aβ42 by itself (Milà-Alomà et al., 2019).While it unfortunately cannot predict and confirm Alzheimer's disease, it may be able to help in detect possible amyloid positive cases (Milà-Alomà et al., 2019). Aβ-related blood biomarkers are arguably the most reliable and promising of all possible biomarkers found in the blood. Keeping all of this in mind, the use of Aβ blood biomarkers is still too unpredictable to use often, and cerebrospinal fluid will continue to be collected and used until more significant advances have been made in this area.

Tau-Related Enzymes

When it comes to testing tau-related proteins from the cerebrospinal fluid, scientists look to find anything similar or related to this in the blood. The answer would be enzymes related to tau pathology. Tau inclusions are found in a wide range of neurodegenerative diseases (Milà-Alomà et al., 2019). When it comes to cerebrospinal fluid, two types of tau are measured; total and phosphorylated. When studied and transferred over to blood, some findings were made possible with the introduction of ultrasensitive assays. With this technology, several studies have shown an increase in the total tau found in their blood as compared to controls (Milà-Alomà et al., 2019). However, the overlapping values in these studies made this technique inefficient for diagnostic use (Milà-Alomà et al., 2019). Additionally, total-tau found in the plasma predicts cognitive decline and the risk of dementia (Milà-Alomà et al., 2019). However, the phosphorylated-tau studies are much more promising. In both plasma and serum phosphorylated tau, significantly higher

amounts have been shown in the blood when compared to controls (Milà-Alomà et al., 2019). Although these are significant advances toward one day using blood for the routine testing of Alzheimer's, there is still much progress to be made.

Inflammatory markers

The degenerating tissue in the brain of an Alzheimer's patient is an easy target for inflammation. That being said, the amyloid deposits building up in the brain of Alzheimer's patients are considered to elicit a wide range of inflammatory responses (Schneider et al., 2009). Furthermore, the proteins associated with said responses are found to be in tight association with the telltale plaques of Alzheimer's (Schneider et al., 2009). However, it still is not clear whether inflammation is important to the development of Alzheimer's, or if it is simply a byproduct that does not alter the course of the disease progress (Schneider et al., 2009).

Early Testing and Diagnosis

Alzheimer's disease currently affects an estimated 5.5 million adults in the United States (Sindi et al., 2015). In this disease, pathological processes start in the brain long before clinical dementia (Mattsson et al., 2010). In order to allow early testing and diagnosis to happen, there must be biomarkers present that will clearly indicate Alzheimer's in an early stage. Although many biomarkers were outlined earlier, few of them allow Alzheimer's' to be accurately detected in its early stages. These markers include Aβ pathology as well as tau-related pathology. However, because there is currently no cure for this devastating disease, the next best track for possible patients is prevention. Early intervention is the optimal strategy because the patient's level of function will be preserved for a longer period of time (Mattsson et al., 2010). Some basic prevention measures one can implement into their lifestyle are eating healthy, introducing more physical exercise, keeping their mind mentally stimulated with work or activities, and reducing alcohol intake (Sindi et al., 2015). The use of drugs for the prevention of Alzheimer's is still being studied, and there are no reliable, accurate findings at this time.

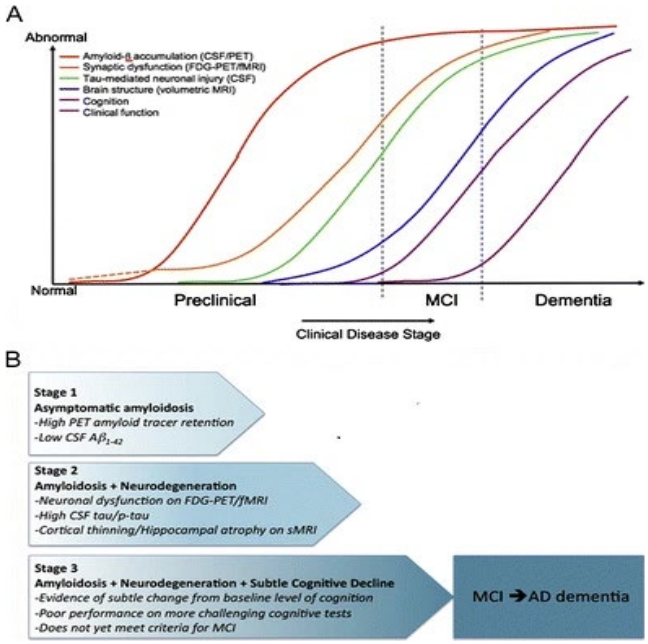

Fig. 4: The different clinical stages of Alzheimer's. As shown, the preclinical stage of Alzheimer's is very long, and can be detected through the use of biomarker testing (Counts et al., 2016).

Conclusion

Early testing of Alzheimer's is necessary for affected patients and is possible through the use of biomarkers. Cerebrospinal fluid biomarkers, including Aβ (1-42) and Tau-related pathology, are the most reliable and widely used markers to diagnose and predict Alzheimer's disease. Studies have begun on biomarkers from the blood; however, they are not as reliable as cerebrospinal fluid, and are still being studied and developed for common use. Blood biomarkers being researched include Aβ-related proteins, Tau-related enzymes, as well as inflammatory markers. Due to the fact that there is still currently no cure for Alzheimer's disease, the next best route is prevention as well as early diagnosis. This effort would be much more successful with the help of primary care physicians. For example, any memory complaints from older patients should be taken seriously and the possibility of Alzheimer's disease should be thoroughly ruled out, instead of quickly dismissed as a symptom of normal aging. Especially if there is a family history of Alzheimer's, and they are likely to have the gene. In the future, this topic may be more saturated with information, once tests are complete on the use of blood in biomarkers, hopefully with multiple successful markers established. Other researchers may also be able to one day build on the possibility of a cure, or even earlier screening for the Alzheimer's gene. Until then, it is important to keep a healthy lifestyle to decrease the chances of Alzheimer's disease and take prevention into your own hands.

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