The Neurological Mechanisms and Possible Treatments of Sporadic Alzheimer's Disease

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AUTHOR BIO

The author of this paper is Jason Zhang, a grade 12 student who is interested in STEM, especially neuroscience. He currently studies in Mulgrave School. As a Canadian, he spent approximately 15 years in Shanghai and moved back to Vancouver with his family in 2020. In middle school, he was exposed to the complexity of the brain and decided to dive deep into the field of memory and neuro-diseases. In the future, he hopes to pursue a career studying neurodegenerative diseases and become a neuroscience researcher.

ABSTRACT

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, accounting for sixty to seventy percent of all causes of dementia. Though Alzheimer's Disease has been discovered for more than 116 years, the disease still lacks effective treatment. This paper presents the history of Alzheimer's disease since 1907, when it was first discovered. As a literature review, the paper explores a wide range of studies conducted by global researchers. The major focus of this paper is to illustrate the specific neurological mechanisms of sporadic Alzheimer's disease by looking into the two most predominant theories: Amyloid Beta Plaques, and Neurofibrillary Tangles. This paper compares and contrasts the two theories and discusses possible directions that could be considered in future studies. This paper also illustrates the potential impact and changes Alzheimer's Disease could have on the brain from a neurology perspective. Besides the pathology of the disease, this paper also reviews possible treatments and ways to prevent Alzheimer's Disease in a variety of areas including lifestyle, diet, hormones, and FDA-permitted medicines.

Keywords: *Alzheimer's Disease, Neurodegenerative Disease, Amyloid Beta Plaques, Neurofibrillary Tangles, Tau Protein Theory, Treatment and medicine, FDA permitted medicine, prevention of Alzheimer's disease.*

INTRODUCTION

Dementia is the general terminology used to describe a set of symptoms including poor memory and difficulty learning new information. In most cases, dementia is associated with damaged brain cells which can be caused by a variety of diseases. Alzheimer's disease (AD) is one of the most common neurodegenerative diseases that starts slowly, but progressively worsens over time. It accounts for sixty to seventy percent of all causes of dementia (Alzheimer's Association, 2022). AD could directly cause degeneration or loss in neurons in the cortex of the brain.

In 1907, German psychiatrist and neuropathologist Alois Alzheimer reported a case in which a 51-year-old female patient exhibited a variety of symptoms of early dementia. This included loss of recent memory, difficulty performing familiar tasks, and some psychiatric disturbance. Four years after the case was reported, the patient died, and this disease was named "Alzheimer's disease." (Castellani, 2010). By 2022, approximately 44 million people worldwide have been diagnosed with AD, and this number will likely triple to 132 million people by 2050 (Alzheimer's Association, 2022). In the United States of America, AD and other dementia-related diseases cost around 321 billion dollars per year. Therefore, AD not only leads to detrimental health outcomes in the patients, but also imposes an economic burden on society. In this paper, I will explore the neurological mechanisms as well as possible treatments of the type of Alzheimer's now known as sporadic.

Two Types of Alzheimer's Disease

After Alzheimer's disease (AD) is discovered in patients, the disease is categorized into one of two clinical conditions based on the different ages of onset. The two clinical conditions have very different impacts on individuals, and the age of onset indicates the possible causes of AD and needs to be treated differently in terms of pharmacology. In the case of the 51-year-old female patient discussed above, due to the early age of onset, this was recognized as the "presenile" type. This type of AD is mostly familial, suggesting that the causing factor of AD can be inherited from ancestry. In contrast, the more common, older age of onset after 65 years old is recognized as the "senile" or "sporadic" type. This type differs from the presenile type by the older age of onset and its low probability of inheritance; thus, sporadic AD is also the more common type (Rolston, 2010).

In terms of clinical presentation, evidence such as memory loss or impairment in at least one other cognitive domain, as well as evidence of social or occupational function disturbance, is required for the diagnosis of AD. More specifically, patients tend to exhibit symptoms based on the time and brain regions affected, such as deteriorating speech ability, personality, judgment, or sometimes vision. Unfortunately, despite all available treatments, clinical AD continues to advance. (Smith, 2010) Over months and years, progressive memory loss continues resulting in a disoriented personality, judgment dysfunction, speech abnormalities, and apraxias. Over time, patients' ability to care for themselves deteriorates. In most cases, pneumonia is the proximate cause of death. This is a devastating illness that strips the patient of their personality and dignity (Castellani, 2010).

Furthermore, AD's impact varies depending on many other factors, such as sex. Females tend to have a higher risk of developing AD and dying from the disease. This is due to the production of estrogen and testosterone (Andrew, 2018). These hormones have

neuroprotective mechanisms that help to counter most neurodegenerative diseases. The male tends to have a higher level of estrogen production than female after females experience menopause which results in this different prevalence rate (Tierney, 2018).

Pathology of Alzheimer's Disease

Although the cause of sporadic AD is not fully understood, the majority of pathology discussion focuses on two theories: the Amyloid-Beta Plaques theory and the Neuron Fiber Tangles theory. These two theories are both well supported by the observation of patients' brain scans.

Amyloid-Beta Plaques Theory

Amyloid precursor protein (APP) is an integral protein that is found in numerous neuron synapse tissues. It is a cell membrane receptor that regulates synapse formation, brain plasticity, antimicrobial activity, and iron export. APP is encoded by the APP gene and is controlled by substrate presentation. After this protein is used, it usually gets broken down and recycled for future use. However, during the process of breaking down the used amyloid precursor protein, different secretases are utilized to break down the APP (Huang, 2012) In normal situations, the APP is broken down into a secreted amyloid precursor, a protein alpha, and an 83 amino acid fragment named CTF 83. This process is catalyzed by the enzyme named alpha-secretase or α secretase. Later, the CTF 83 compound is further cleaved by gamma-secretase, which is made up of PEN-2, Aph 1, NCT, etc. (Hansson, 2004). This cleavage results in an APP intracellular domain, which is an AICD domain that enters the nucleus and drives the neuroprotection pathways. The remaining sAPPα is secreted from the neuron and enables learning and memorizing (Castellani, 2010).

In contrast, AD patients go through a different process. For patients with AD, instead of alpha-secretase, beta-secretase is used to cleave the amyloid precursor protein into CTF 99 (carbon terminal fragment). The gamma-secretase cuts the CTF 99 compound into an AICD domain and an Abeta 40/42 peptide. The Abeta 40/42 peptide, together with APOE, forms insoluble amyloid-beta plaques(Murphy, 2010). Formed outside of neurons, these plaques block the neuron signaling interaction, which impairs memory ability. The plaques then result in inflammation that damages surrounding neurons and eventually becomes a neurodegenerative disease (Castellani, 2010).

Neurofibrillary Tangles and Tau Protein Theory

In contrast to the Amyloid-Beta Plaques Theory, the Neurofibrillary Tangles and Tau Protein Theory (TAU) suggests that the trouble might be within the neurons instead of outside the neurons(Castellani, 2010). Microtubules help transport nutrients and maintain the shape of the neurons, and Tau proteins are a collection of six highly soluble proteins that play an essential role to maintain the integrity of these cellular microtubules (Arendt, 2016). In the case of AD, after amyloid-beta plaques are built, the enzyme kinase is activated and it phosphorylates the Tau protein. The Tau protein then leaves the microtubule and starts to clump up with other phosphorylated Tau proteins which eventually results in neurofibrillary tangles. In AD patients, due to the absence of Tau protein in the microtubules, the microtubules can no longer transport nutrients around neurons (Rolston, 2010). This leads to apoptosis (programmed cell death). As more neurons start the apoptosis process, neuron signaling is significantly

impaired and the gyri shrink, which results in severe AD.

External Factors Associated with Alzheimer's Disease

There are numerous external factors that could lead to AD. Though these hypotheses have not been fully proven, these risk factors show a high correlation to the presence of sporadic AD. As previously mentioned, despite the genetic factors that affect the possibility of getting AD, the most significant factor is still age. Between the ages 60-65, AD tends to affect 1% of the total population. The risk increases to nearly 50% of the age group over 85. Using France as an example, in 2019, around 5800 citizens within the age range of 55 to 64 were diagnosed with AD. The number increased to 34800 confirmed cases in the age group of 65 to 74 and reached 404,000 cases in the age group of 75 to 84 (Ameli, 2021).

The second factor is the genetic component of AD. Genetics play very different roles in sporadic and familial AD. In terms of early-onset, presenile or familial cases, the genetic components focus on chromosomes 21, 19, 14, and 1 (Castellani, 2010). These chromosomes are inherited from the ancestry history of the family. In contrast, sporadic or senile AD are usually affected by the e4 allele of the apolipoprotein E gene (APOE 4). APOE gene is a cholesterol gene that usually has three forms. The first form is APOE 2, which appears to reduce the risk of AD. The second form is APOE 3, which does not affect the risk of AD. The third form is known as APOE 4, which seems to increase the risk of AD. The three proteins have different sequences by amino acid substitution at different residues(Huang, 2012). Single inherited APOE 4 slightly increases the risk of AD, while two inherited APOE 4 increases the risk of AD to a greater degree. APOE 4 carries the least cholesterol to the neurons in the three forms of apolipoprotein. In addition, APOE 4 degrades quicker, and its ability to clean amyloid-beta is weaker(Mucke, 2012). As a result, the presence of APOE 4 potentially leads to a higher amount of amyloid-beta plaques.

Treatments of Alzheimer's disease

Though AD was discovered around 115 years ago, there is still a lack of effective treatment. As mentioned above, Alzheimer's disease tends to be a progressive disease whereby once the patient starts exhibiting symptoms of AD, it is usually at a very late stage that synapses function is largely impaired. Thus, most drug developers aim to make drugs or treatments that prevent Alzheimer's disease from progressing into late stages, which also means targeting the formation period of Amyloid Beta Plaques. On the other hand, much of modern pharmacology attempts to slow the progress of the disease. An example of such a treatment is Aducanumab. These types of drugs delay the clinical decline by targeting beta-amyloid plaques and removing ABP to slow down the rate of forming clumps and inflammation. This can successfully delay the formation of amyloid-beta plaques, which leads to a delay in clinical decline (Alzheimer's associations, 2021). By removing some of the amyloid-beta plaques formed around the neurons, the synapse signals will be able to transfer from dendrites to dendrites and perform basic cognitive functions.

The other approach is to treat the symptoms of AD. This alternative approach can temporarily mitigate some symptoms of AD. FDA has also approved drugs that focus on the two categories of symptoms, one being cognitive symptoms, including memory and thinking, and the other being non-cognitive symptoms, including behavioral and psychological symptoms. In terms of cognitive symptoms,

FDA has approved drugs like cholinesterase inhibitors and glutamate regulators to treat symptoms related to the cognitive system(Alzheimer's association, 2021). These cholinesterase inhibitors can prevent the breakdown of acetylcholine and support the neurotransmission process. Glutamate regulators on the other hand improve cognitive systems by regulating glutamate, which is a chemical messenger that helps to process information in the brain(Alzheimer's association, 2021).

Despite the pharmacological treatments that were approved by FDA, there are many other treatments or therapies available now that seem to have an impact on AD. One example is hormone replacement therapy. As mentioned above, estrogen tends to lower the risk of AD because of three processes. Estrogen helps to maintain cerebral blood flow, reduce oxidative stress and decrease the formation of amyloid-beta(Andrew, 2018). Population-based studies (Castellani, 2010) have suggested such hormone replacement therapy may delay the onset of Alzheimer's disease.

Another treatment, or method, to reduce the risk of Alzheimer's disease is known as the Mediterranean diet. Many studies have shown that this diet tends to correlate to the risk of AD. The Mediterranean diet is well known for its "high intake of vegetables, fruit, and cereals; low to moderate intake of saturated fat, high intake of fish and low intake of dairy products and a moderate amount of ethanol" (Rolston, 2010). Many theories and studies have suggested that vitamin deficiency could potentially result in a higher risk of AD. Thus having high levels of vegetable intake, such as kale, could help people avoid vitamin deficiency, resulting in a lower risk of AD.

Another possible approach is anti-inflammatory drugs, sometimes referred to as non-steroidal anti-inflammatory drugs. As previously mentioned, when amyloid-beta plaques progress to the state of interrupting neurotransmission, inflammation in neurons damages surrounding blood vessels. Recently, there have been many observations (Smith, 2010) that there is a lower than expected prevalence rate of Alzheimer's disease in patients with rheumatoid arthritis. As observed, the long-term treatment of anti-inflammatory drugs might be protective against the development of Alzheimer's disease. The anti-inflammatory treatments can reduce the decline of microglia, astrocytes, and the production of amyloid-beta plaques. According to the Cache County Study on Memory Health and Aging (2013), treatments like NSAIDs could potentially prevent cognitive function decline at a relatively earlier age of onset. On the other hand, in most trials, NSAIDs did not showcase a significant positive impact on the development of sporadic Alzheimer's disease cases. In short, the extent to which anti-inflammatory drugs are effective remains a controversial question that future research could focus on (Castellani, 2010).

Conclusion

In conclusion, though sporadic Alzheimer's disease was discovered over 100 years ago, modern neuroscientists have not yet discovered any effective treatment that targets this disease. The greatest hindrance is a lack of knowledge about the causes of the disease. Until now, there are only hypotheses like Neurofibrillary Tangles and Tau Protein Theory and Amyloid Beta plaques. These hypotheses have been supported in numerous experiments, research, brain scans, and studies, but the methods of treating TAU tangles and Amyloid Beta plaques remain a mystery. Since 1985, most neuroscientists have focused on the amyloid-beta plaques theory. However, they have failed to conquer the disease by only targeting amyloid-beta plaques. In the future, research should begin to shift its focus towards

TAU tangle theory. If this attempt also fails, other treatments will have to be considered.

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