University of Nevada, Reno

Alzheimer's Disease: An Introduction to The Disease, its Mechanisms, and a Clinical Case Study

A thesis submitted in partial fulfillment of the requirements for the degree of Bachelor of Science in Neuroscience, the BSMD program, and the Honors Program

By

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Table of Contents

List of Figures

Chapter 1

Alzheimer's disease: A look at Clinical Features and Underlying Mechanisms

Abstract

Alzheimer's disease is the leading cause of dementia, and it has a high prevalence in western societies. As people are living longer, dementia has become a growing concern particularly for the elderly population. More research is being conducted to better understand Alzheimer's in an effort to cure it. Presently, there is no known cure for the disease, and no consistently effective treatments that halts the progression of the disease. Clinical features, pathophysiology, and epidemiology are explored along with potential causes, methods of diagnosis, and current treatments. New research containing potential future directions for the development of treatments will also be discussed.

Clinical Features

Early detection of Alzheimer's is next to impossible because there are no reliable and valid preclinical symptoms of the disease. Once symptoms for Alzheimer's can be accurately detected, there is already irreparable damage to the brain. For a person to be diagnosed with dementia, cognitive impairment must not only be present, but severe enough to interfere with a person's ability to complete everyday activities. The clinical course of Alzheimer's demonstrates the expanding neuropathy of the disease. Although the preclinical stage can't be detected using current technologies, research suggests that the preclinical stage may begin several decades before diagnosis. Once diagnosed, the stages of dementia are broken up into mild, moderate, and severe based on a person's

ability to maintain independence. After diagnosis, the average survival time ranges from five to eight years (Förstl & Kurz, 1999).

The pre-dementia stage of Alzheimer's can show mild cognitive impairment for up to five years before dementia is officially diagnosed. The difficulties faced by patients in the pre-dementia stage include some trouble acquiring new information, planning, and problems accessing semantic memory. Furthermore, ability to perform complicated tasks may be reduced. During this stage, individuals do not have trouble with day to day activities, and memory aids may help to overcome cognitive deficits. In addition to minor cognitive impairments that are potentially present during the pre-dementia phase, individuals may experience feelings of withdrawal or depression (Förstl & Kurz, 1999).

During the mild dementia stage, the prominent feature is a significant deficiency in memory and learning. The type of memory that is most negatively impacted during this phase is recent declarative memory. Most other types of memory are impacted to a much lesser degree if they are impacted at all. Individuals begin to have difficulty completing day to day activities because of these memory impairments. They may also find it difficult to plan, organize, make judgments, and do complex chores. Communication may also be inhibited due to a diminishing vocabulary, and spatial disorientation may be observed resulting in complications with driving. Therefore, it is not recommended that Alzheimer's patients continue to drive once they have received their diagnosis. At this stage of the illness, supervision is not necessary, but patients may require support with certain basic living and self-care tasks. It is common for patients to begin displaying

depressive episodes in this phase, and this could be attributed in part to loss of freedom due to reduced abilities that result from the neurodegeneration (Förstl & Kurz, 1999).

The moderate dementia stage is characterized by a severe deficiency in recent memory that often causes individuals to live in the past. Impairments in language also become more prevalent. Patients gradually lose the ability to take care of themselves and their households, and eventually lose the ability to recognize familiar faces. Many go on to develop delusions and/or hallucinations caused by cognitive deficits and the underlying processes of the disease. Additionally, patients start to lose emotional control at this stage, and have extreme reactions to minor distress. At this point, patients need close supervision because they are incapable of handling legal and financial issues. Furthermore, household appliances become a source of danger, and there is an increased risk for falling and getting lost in the community. Strain is put on caretakers because individuals in this stage also demonstrate aggressive behavior (Förstl & Kurz, 1999).

The final stage of Alzheimer's is the severe dementia phase. At this point, patients suffer major impairment of all cognitive function. Language is reduced to words or phrases, the circadian rhythm becomes completely disrupted resulting in restlessness and aggression, basic motor functions such as chewing are impaired, and patients display extreme apathy. Frontal lobe atrophy can also be observed in brain imaging. During this phase, individuals are in need of comprehensive nursing care and cannot see to their basic needs. Clinical diagnosis of Alzheimer's disease lowers the life expectancy of an individual by one-third. The most frequent cause of death in Alzheimer's patients is pneumonia followed by myocardial infarction and septicemia (Förstl & Kurz, 1999).

Pathophysiology

Imaging of Alzheimer diseased brains has shown that amyloid clumps form plaques in the brain which cause a loss of neurons in the vicinity of these plaques. Although some characteristics of Alzheimer's are apparent in brain imaging, there is no specific feature in the brain indicative of Alzheimer's. Usually atrophy can be observed, and the atrophy is almost always symmetric. Dilated frontal and occipital poles of the lateral ventricles can also usually be observed. Not much is known regarding the relationship between amyloid plaque formation and neural death. However, it is widely hypothesized that beta-amyloid plaques are the principle cause of the cognitive impairments that occur in Alzheimer's disease (Reference, 2014).

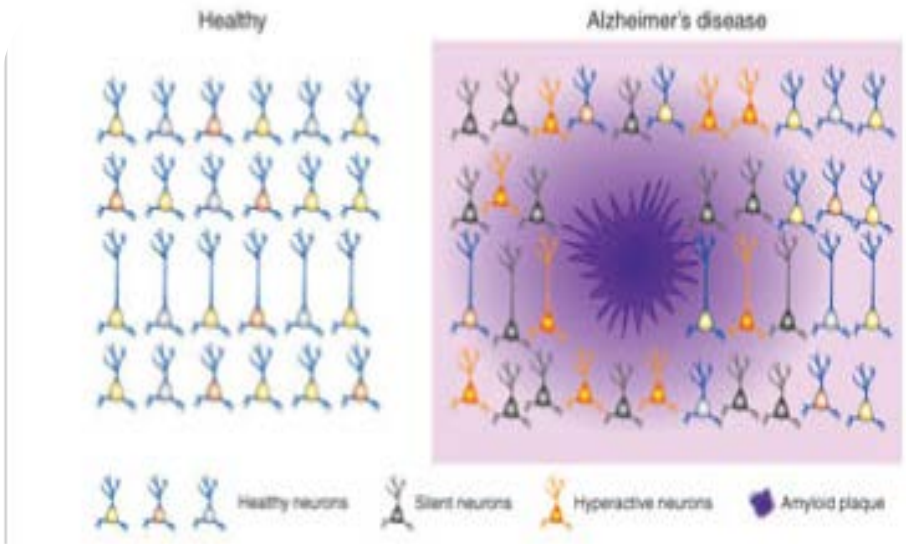

FIGURE 1: Illustration of beta amyloid plaques. This illustration shows how amyloid plaques cause neuron loss in Alzheimer's disease (Reference, 2014).

As a person ages, mutations in proteins that are needed for normal amyloid formation lead to the prevalence of plaques. Since these amyloid plaques cause neurodegeneration to nearby neurons, they result in decreased cognitive brain function. As the patient loses more and more neurons to these amyloid plaques, they develop dementia which is the defining characteristic of Alzheimer's disease. Once the dementia stage has begun, life expectancy is greatly decreased as there is no current treatment that can reverse the neurodegenerative effects of the plaques (Blennow, de Leon, & Zetterberg, 2006).

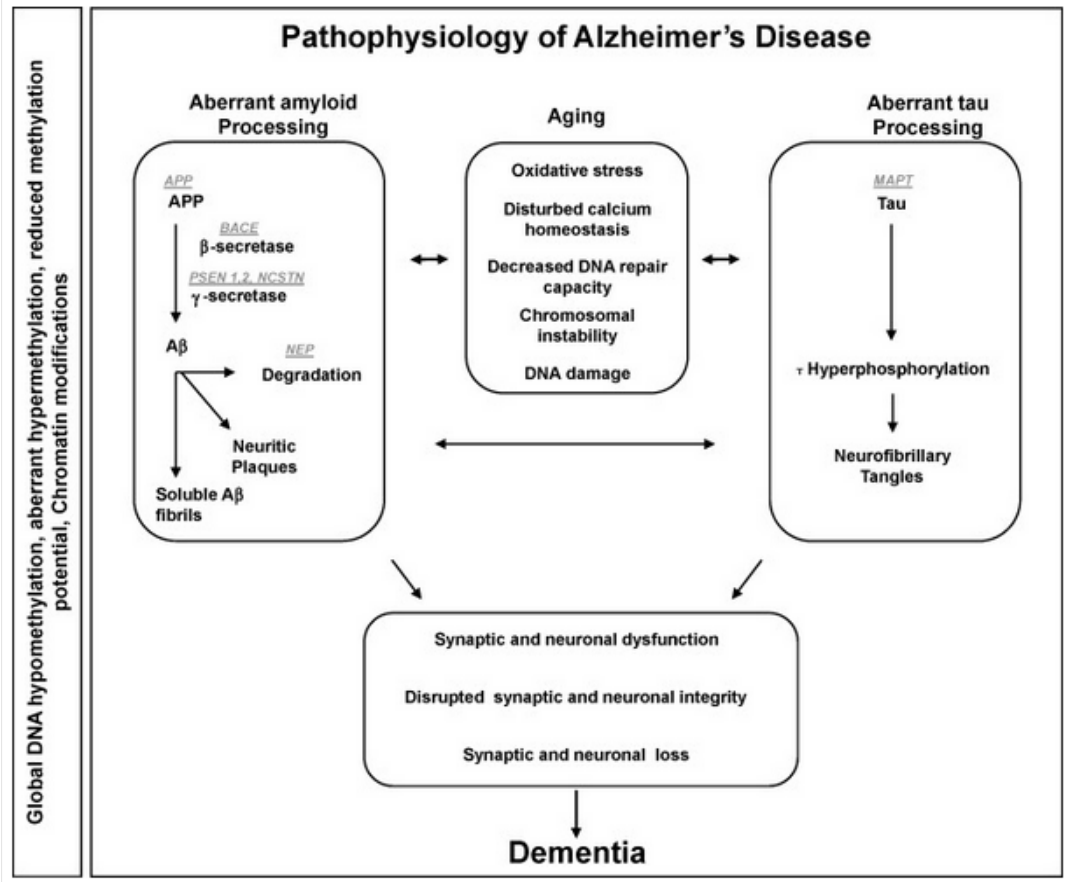

Figure 2: Flow chart of pathophysiology. This flow chart summarizing the pathophysiology of Alzheimer's shows how issues with the amyloid proteins in conjunction with issues that arise normally in the aging process go hand in hand in causing dementia (Chouliaras et al., 2010).

Symptoms

The defining symptom of Alzheimer's disease is dementia, but other core symptoms of the disease include depression, psychosis, and apathy. People with Alzheimer's characteristically display memory issues which are a precursor to dementia. The severity of the Alzheimer's symptoms illustrate the progression of the disease. The more severe the symptoms are, the faster the patient is experiencing the cognitive decline that results in loss of independence and eventually death. Apathy and depression are generally described together in cases of Alzheimer's disease. It is the combination of these two symptoms that can be used to indicate the progression of the disease and allow health professionals to differentiate between the different stages of Alzheimer's. Apathy, which is defined as a group of motivational deficits, leads to loss of goal oriented emotion, motivation and cognition. Apathy may also be a precursor to aggression which is another symptom that occurs as Alzheimer's progresses. Agitation and aggression are very common in patients in the later stages of the disease, and the greater the intensity of the dementia the higher the incidence of aggression in patients. Psychosis is the final of the characteristic Alzheimer's symptoms, and like agitation, is only prevalent in later stages of the disease. Like the other symptoms of Alzheimer's, psychosis is a result of the cognitive deficits caused by loss of synapses. Psychosis in Alzheimer's includes delusions and hallucinations, and this is typically the most severe of all the symptoms associated with the disease (Li, Hu, Tan, Yu, & Tan, 2014).

The symptoms of Alzheimer's are not only predictive of the progression of the disease, but also correlate to imaging of the brain that shows loss of brain volume. Therefore,

treating the symptoms separately is an ineffective focus of treatment. Treating the underlying source of the neuron loss is the only way to slow down the progression of the disease and in turn alleviate symptoms (Li et al., 2014).

Epidemiology

Alzheimer's disease is the leading cause of dementia, and the corresponding neurodegeneration is marked by memory loss and cognitive impairment. It is a growing concern globally as populations age, and the average life expectancy continues to increase. Alzheimer's affects approximately six percent of the population, is of particular concern in the countries of North America and Europe which report the highest prevalence of the disease. Those who report the highest rates of Alzheimer's are members of the elderly population, and those who are at highest risk of developing Alzheimer's are people who are aged sixty-five and older. There are presently 24 million cases of Alzheimer's worldwide, and this number is expected to double every twenty years. It is estimated that there are approximately 4.6 million new cases of the disease diagnosed annually. Alzheimer's is a growing concern because the underlying mechanisms of the disease are not fully understood, and there are no known treatments. Furthermore, treatments that target symptoms have shown only limited success so those suffering from the disease have a decreased standard of life in addition to a decrease in life expectancy. It is for these reasons that Alzheimer's treatment is a burgeoning area of research (Reitz, Brayne, & Mayeux, 2011).

Genetics

Although the sporadic form of Alzheimer's is by far the most common, there is a growing body of research that points to genetics as a potential cause of the more rare familial type of Alzheimer's disease. While there has not yet been one single gene or a group of genes that have been definitively identified as a cause for the disease, those who believe genes play a role in Alzheimer's say genetic factors affect dendritic structure and function, so genetic mutations may likely be an underlying cause of the disease. The consensus regarding genetics in relation to AD suggests that a genetic mutation or genetic variant in the amyloid protein results in plaques and neurofibrillary tangles. In the sporadic type of Alzheimer's, many different genes are being studied, but there is no conclusive genetic cause and the mutations may just be a result of the normal aging process. Also, the many different genes could all interact with environmental factors to result in the onset of the disease. However, in the familial type, two main genetic mutations have been identified. The first is on the amyloid precursor protein gene on chromosome 21, and the second type is a mutation on the presenilin 1 and 2 genes. Of the two types, the mutations on the presenilin genes are more common. However, the sporadic form of the disease makes up the bulk of diagnosed cases (Chouliaras et al., 2010).

Environmental Factors

There has not been any conclusive scientific evidence that environmental factors cause or worsen Alzheimer's. Smoking and diabetes have been linked to the increased prevalence of the disease, but a causal relationship has not been established. There has been some research indicating dietary modifications could reduce the risk of Alzheimer's, but there is no consensus around what diet effectively minimizes risk of Alzheimer's. In fact,

dietary recommendations are contradictory in different articles. One article recommends wine as a way to decrease risk of Alzheimer's, while another lists alcohol as a neurotoxin that could contribute to AD symptoms. Some researchers say obesity is a risk factor, but others recommend increased intake of unsaturated fatty acids as a way to minimize risk factors associated with Alzheimer's. Although it is widely hypothesized that environmental factors may contribute to the incidence or progression of Alzheimer's disease, there is not presently enough research to positively identify what the specific environmental risk factors are (Plains & Lindsay, 1994).

Diagnosis

In the diagnosis of Alzheimer's, psychiatric analysis and neuroimaging are used in conjunction to isolate AD as the cause of the symptoms presented. Initially, the psychiatric analysis conducts memory tests to gain objective signs of memory loss. After memory loss has been ascertained, neuroimaging such as CT and MRI are performed to verify whether or not the cognitive impairment is due to Alzheimer's. There are many potential causes of dementia, so it is somewhat tricky to isolate Alzheimer's as the cause. Doctors essentially have to exclude all alternative causes of dementia before arriving at an Alzheimer's diagnosis. Cerebral atrophy and white matter lesions are necessary to prove Alzheimer's, but these characteristics don't have much diagnostic value since any form of dementia would present similar atrophy. Since the criteria for diagnosis of Alzheimer's was published over twenty years ago and relies on disproving other causes of dementia, the accuracy of diagnosis is relatively low. Sensitivity is around 80%, and specificity is around 70%. These figures are probably even lower in cases of mild

Alzheimer's disease and in primary care settings. Another confounding area in the diagnosis is the concurrence of Alzheimer's and other forms of dementia. The guidelines don't specify methods of diagnosis of Alzheimer's in the presence of other types of dementia (Blennow et al., 2006).

The only definitive way to diagnose Alzheimer's is through neuropathology which can only happen in a postmortem analysis. In the neuropathological analysis, the presence of significant amyloid plaques and neurofibrillary tangles in addition to loss of brain mass near these plaques can lead to a positive diagnosis of Alzheimer's disease (Förstl & Kurz, 1999).

Treatment

Currently, there are no known treatments that reverse or slow down the progression of Alzheimer's disease. In most cases, symptoms of the disease are targeted to improve the quality of life for the patients. Many drugs for the treatment of symptoms have been approved for use, but even these have had limited success since the root cause of the symptoms is not being addressed. One popular treatment is the use of an acetylcholinesterase inhibitors to treat symptomatic memory loss and mild cognitive impairment. This treatment attempts to slow down the loss of cholinergic neurons vital to memory by allowing for ample supply of acetylcholine. Acetylcholinesterase inhibitors have shown modest positive results on cognition in milder cases of Alzheimer's, but the reduced progression of the disease was not long term. In fact, the results did not last past three years of the treatment (Blennow et al., 2006).

Another treatment that has shown some amount of success is Memantine which is meant to improve cognition and alleviate behavioral symptoms by protecting neurons from glutamate mediated excitotoxicity. In cases of moderate to severe Alzheimer's. Memantine showed most significant results of cognitive improvements when paired with an acetylcholinesterase inhibitor. Vitamins B12, B6, E and dietary unsaturated fats are also believed to improve cognitive performance, but there is not enough data to conclusively prove this (Blennow et al., 2006).

Behavioral symptoms such as aggression, apathy, depression, and psychosis can be treated with varying degrees of success using traditional antipsychotic drugs such as Risperdone. Non-steroidal inflammatory drugs are used to treat the inflammation in the brain near plaques, but the efficacy of this in combatting the disease is unknown because the inflammation has not been positively linked to neurotoxicity (Förstl & Kurz, 1999).

Body of Review

The amyloid plaque theory as the cause of neurodegeneration in Alzheimer's disease is widely accepted, however there is still some debate as to what causes the plaque formation. There have been genetic, environmental, and dietary causes proposed, but at the end of the day there just is no conclusive data that paints a clear enough picture of the molecular mechanisms of Alzheimer's. Since the mechanisms are still unknown, treatments have not been developed that successfully target the underlying cause of the disease (Prins & Scheltens, 2013). Current treatments focus on symptom management based on the mechanisms that are believed to be involved. However, new treatments are being studied that target the beta-amyloid plaque formation in an effort to limit

neurodegeneration and stop the progression of the disease. The level of success of these treatments can impart crucial knowledge regarding Alzheimer's because they can help determine if the amyloid theory of Alzheimer's is correct, or if the beta amyloid plaques are just another symptom of a complex neurodegenerative disease (Blennow et al., 2006).

Conclusions

As people continue to live longer, the population that is at risk for developing Alzheimer's disease continues to grow. This debilitating disease is a growing concern because so little is known about the underlying mechanisms. With this deficit in understanding of how the disease works comes a deficit in effective treatment options for those who suffer from the disease. Currently, there isn't even a proven method to help alleviate the symptoms of the disease, much less cure it altogether. Once the disease begins to run its course, the patient not only has a decreased quality of life, but their life expectancy also decreases. This is a problem not only for patients who have no alternatives but to slowly lose all cognitive abilities before eventual death, but it is also a problem for caretakers who have few tools to help them deal with patients who pose a danger to themselves and others due to cognitive impairment and behavioral disorders such as aggression (Li et al., 2014).

Continued research regarding Alzheimer's is a must considering how many lives are impacted as a result of the disease. Once the mechanisms that result in the neurodegeneration are fully understood, it will be easier to design drugs to target those specific mechanisms. There are some promising new treatments being developed and tested along with a lot of time and money being poured into Alzheimer's, so the disease

is being given its due diligence, and there is hope that there will eventually be some way to help people reverse the debilitating effects of the disease.

Chapter 2

Monoclonal Antibody Mediated Amyloid Plaque Removal as Potential AD Treatment

Abstract

Since there are currently no treatments that have been found to reverse the effects or slow the progression of Alzheimer's Disease, there are a wide array of new treatments that are being tested. Since the beta amyloid plaques are widely hypothesized to be the cause of neurodegeneration in Alzheimer's, treatments that target the beta amyloid pathway have grown in popularity. The molecular pathway discussed below aims to use monoclonal antibodies to target amyloid beta peptides, and stop plaques from forming. This approach has shown success in decreasing amyloid plaques, and improving cognition in mice models. Several clinical trials are being conducted to see if the antibodies will yield the same results in humans.

Introduction

The amyloid beta peptide is widely believed to cause many of the symptoms that occur in Alzheimer's patients. Amyloid plaque buildup results in synaptic dysfunction and neurodegeneration. The loss of neurons and synapses manifests itself into loss of cognitive abilities such as memory. Since this has been established, any treatment that wishes to address the underlying cause of Alzheimer's disease needs to combat the amyloid plaque formation that causes neurodegeneration by stopping the aggregation of beta amyloid in the brain. Otherwise, one would simply be treating symptoms without

targeting the underlying mechanisms that cause the disease, and any positive results would be short-lived (Lee et al., 2006).

New trends in treatment development for Alzheimer's propose disrupting parts of the neuropathology of the AD process by using monoclonal antibodies that target beta amyloid. It is hypothesized that the monoclonal antibodies can somehow stop the amyloid cascade by preventing the aggregation of beta amyloid peptides, thereby preventing neurodegeneration. This in turn will prevent the cognitive decline that causes dementia and other symptoms in those with Alzheimer's disease (Prins & Scheltens, 2013). Research has shown that the use of monoclonal antibodies not only slows down neurodegeneration, but may also reverse the cognitive deficits caused by the disease by helping to restore neural function (Lee et al., 2006).

Methods

The first experiment tested the effects of monoclonal antibodies on mice models. They began their experiment by injecting the mice with emulsified beta amyloid. Then, monoclonal antibodies were generated using the Aβ that was injected into the mice as antigens. ELISA plates were used to help quantify the amounts of Aβ protein after the mice were given the monoclonal antibodies. ELISA plates are tests that use the presence of antibodies to detect the presence of a substance, which was in this case, beta amyloid protein. The concentration of Aβ was determined by using horseradish peroxidase-conjugated m266 (anti-Aβ13–28) as a reporting antibody. These antibodies do not recognize the N terminus of Aβ, so they did not compete with NAB61 which was the

monoclonal antibody used to attack Aβ and stop the plaques from forming (Lee et al., 2006).

To determine whether immunization improved learning and memory in the mice, 17–19-month old litter mates who had of amyloid plaque formation in their brains were given an initial dose of 400 μg of NAB61 followed by maintenance doses of 200 μg. Mice were then subjected to the visible platform Morris Water Maze experiment in which their ability to reach a visibly marked platform was measured during six training blocks (four trials/block, two blocks/day). Mice were then observed as they attempted to locate the hidden platform over a period of 9 days. Three trials tested the visual reference memory of the mice by removing the hidden platform and recording swimming behaviors. Data was recorded using a video tracking system. Mice then underwent biochemical and histological assessments in which their brain tissue was analyzed. To determine whether passive immunization removed the Aβ plaques, the mice were killed three days after completing the platform experiments so brain tissue could be analyzed. Changes in Aβ deposits and amounts in the mice brain tissue were measured by ELISA analyses (Lee et al., 2006).

In the second experiment, monoclonal antibodies were also used to test the effect they have on amyloid aggregates. Some similar methods were used including the ELISA stain to analyze the quantity of amyloid deposits, but different monoclonal antibodies was used. Although the monoclonal antibodies that were used were different, both experiments were centered on the theory that amyloid deposits are the main source of neurotoxicity in Alzheimer's, so treatments should target the amyloid deposits.

To begin, two commercially available monoclonal antibodies were raised to target beta amyloid peptides. The two antibodies used in this experiment were mAB 6F/3D and mAB AMY-33. Next, in vitro aggregation of beta amyloid was induced followed by introduction of the two monoclonal antibodies. The amounts of the antibodies vs antigen (beta amyloid) were equimolar in one experiment, but in a different experiment excess amounts of the antibodies were used. The idea behind this experiment was that the antibodies should break up and denature the beta amyloid in the test tubes, and the amount of beta amyloid left in solution under the various conditions could be determined using ELISA assays (Solomon, Koppel, Hanan, & Katzav, 1996).

In the ELISA tests, bound monoclonal antibodies were measured. The amount of monoclonal antibody bound was assumed to be proportional to the amount of soluble amyloid peptide that remained in the reaction tube after incubation in the various conditions used during the experiment. The amount of beta-amyloid left in the test tubes indicated that the antibodies where successful in breaking down amyloid peptides (Solomon et al., 1996).

Results

Introducing monoclonal antibodies has shown some success in diminishing amyloid plaque formation in mice models and laboratory experiments. Less plaque formation has been shown in instances where monoclonal antibodies were introduced, so beta-amyloid plaque formation was disrupted by the antibodies (Lee et al., 2006). However, the antibodies weren't always successful in detecting and destroying amyloid aggregates, and they sometimes can only recognize specific conformations of beta amyloid. In cases

where the antibodies have been successfully neutralized, research has shown that memory and learning impairments can be reversed (Lee et al., 2006). The key findings by both studies are summarized below using figures from the original journal articles.

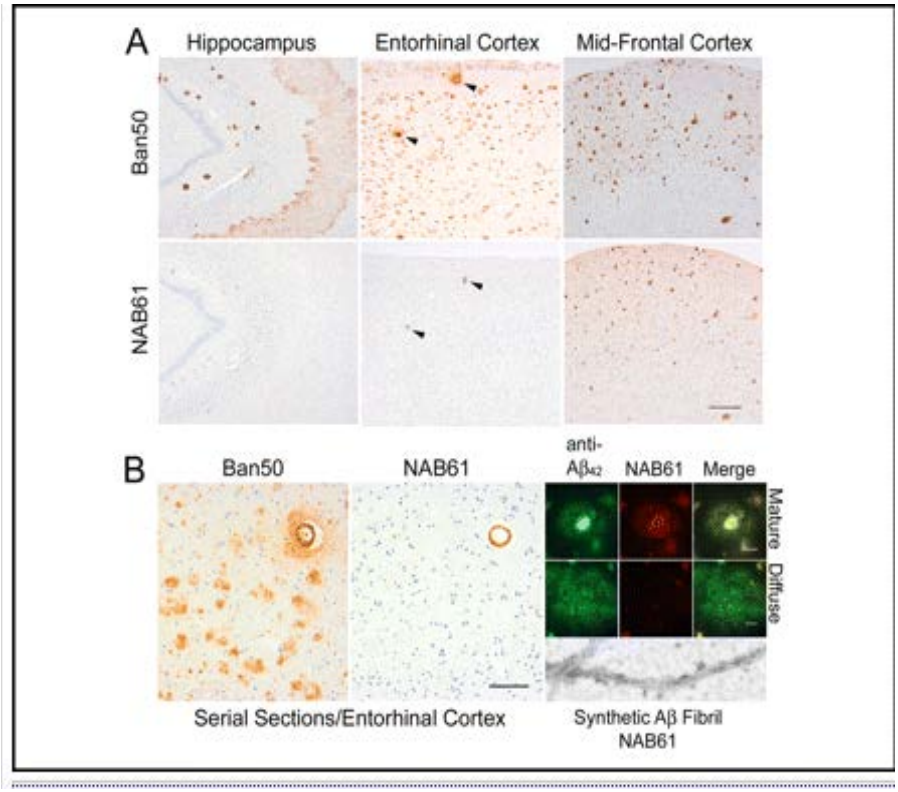

FIGURE 3: Effects of monoclonal antibody NAB61 on plaques. The figure above, from the first experiment, demonstrates that the monoclonal antibody NAB61 only recognizes the conformation of amyloid beta proteins that are found in the more advanced pathological deposits of amyloid beta. This explains why the picture shows varied antibody response in the different areas of the brain. In instances of Alzheimer's, limbic regions of the brain are least affected by the neurotoxic plaques, so less of the monoclonal antibody was visible in those brain tissue samples. In areas of the brain that are heavily affected by the mature amyloid plaques such as the mid-frontal cortex, there was a higher prevalence of the monoclonal antibody, so the antibody is successful at targeting the more damaging beta amyloid aggregates (Lee et al., 2006).

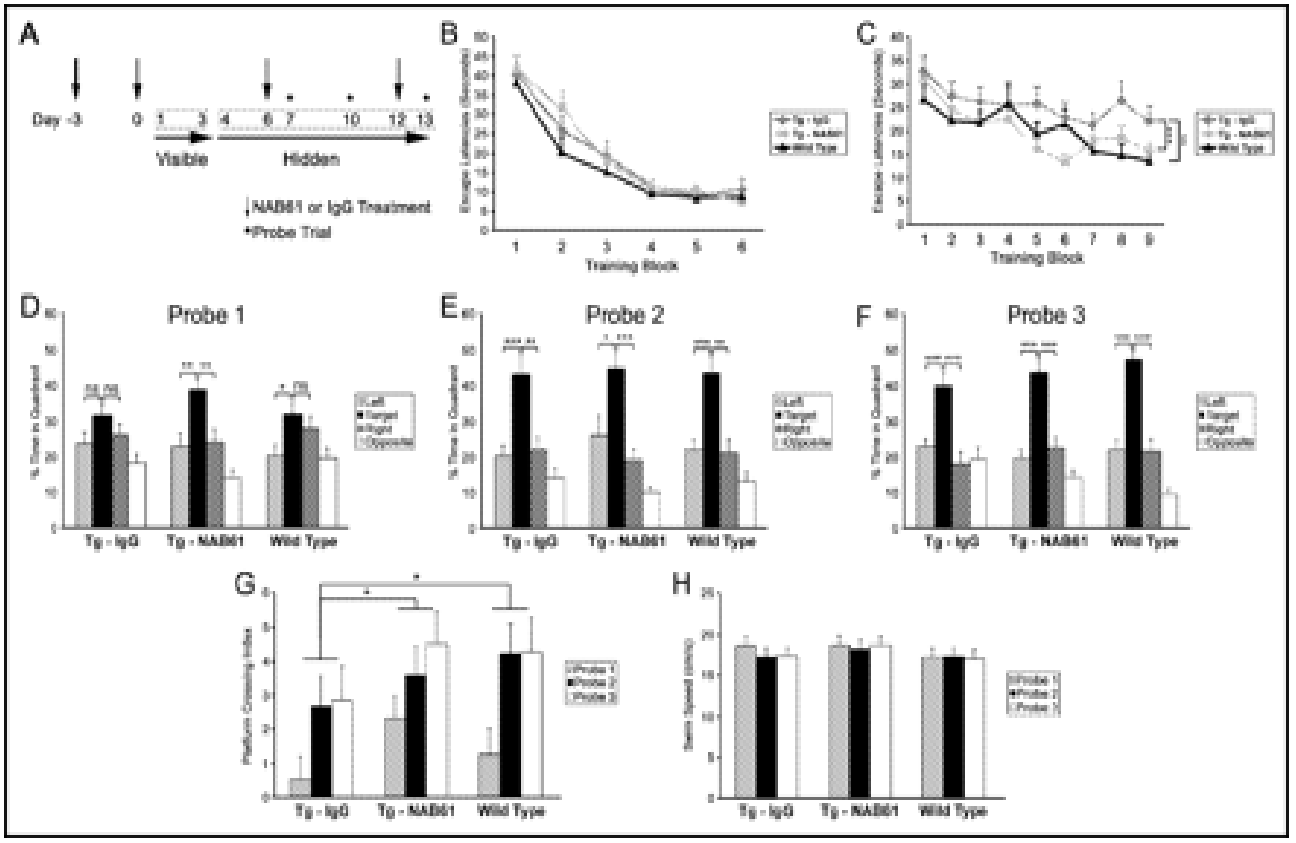

FIGURE 4: NAB61 effect on memory. The monoclonal antibody NAB61 was also shown to improve spatial learning and memory in addition to targeting amyloid aggregates. The antibody was administered to mice who had amyloid aggregates, and they were put in the water maze to test their memory formation. After several days, the monoclonal antibodies were shown to be able to neutralize the amyloid deposits, and the mice showed improved results in the memory task. This demonstrates that targeted removal of monoclonal antibodies may help to alleviate cognitive dysfunction caused by amyloid plaques (Lee et al., 2006).

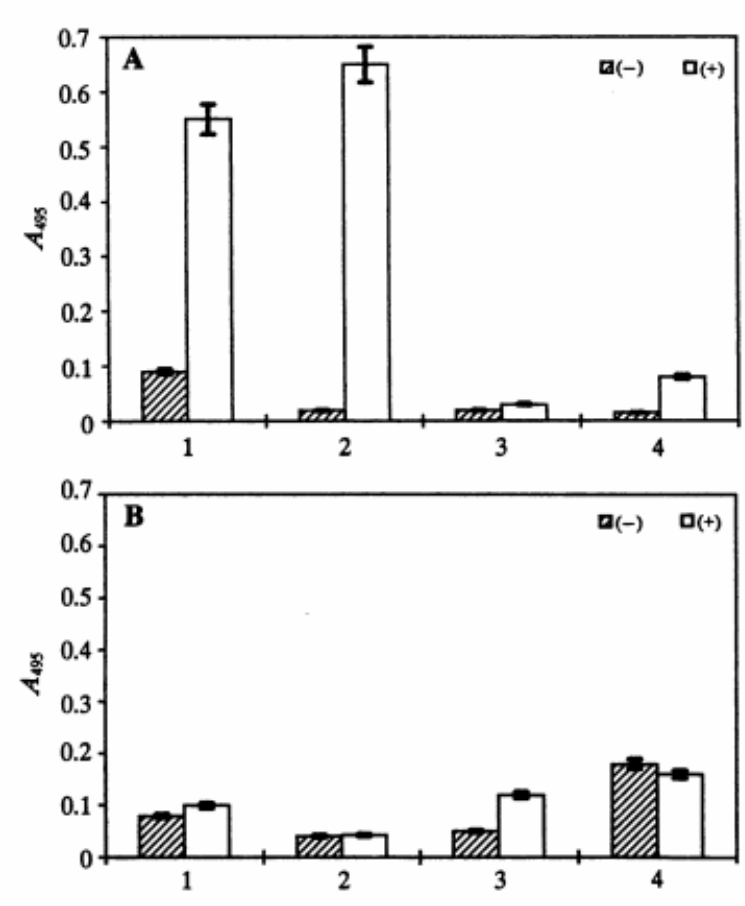

FIGURE 5: Effects of mAB6F/3D and mAB AMY-33 on amyloid plaques. The figure above is from the second experiment that tested the effects of monoclonal antibodies in vitro. It shows the amounts of soluble beta amyloid in the absence (-) or presence (+) of the two monoclonal antibodies mAB 6F/3D and mAB AMY-33 as measured by the ELISA analysis. The monoclonal antibody AMY-33, which recognized specific amino acid residues in beta amyloid, inhibited the aggregation of peptide in the presence or absence of heparan sulfate. No inhibitory effect was found in metal-induced amyloid aggregation under the same experimental conditions. The monoclonal antibody 6F/3D, which recognizes an epitope of beta amyloid, slightly interfered with aggregation caused by Zn2+. However, it had no statistically significant effect on the aggregation induced by other aggregation-inducing agents (Solomon et al., 1996).

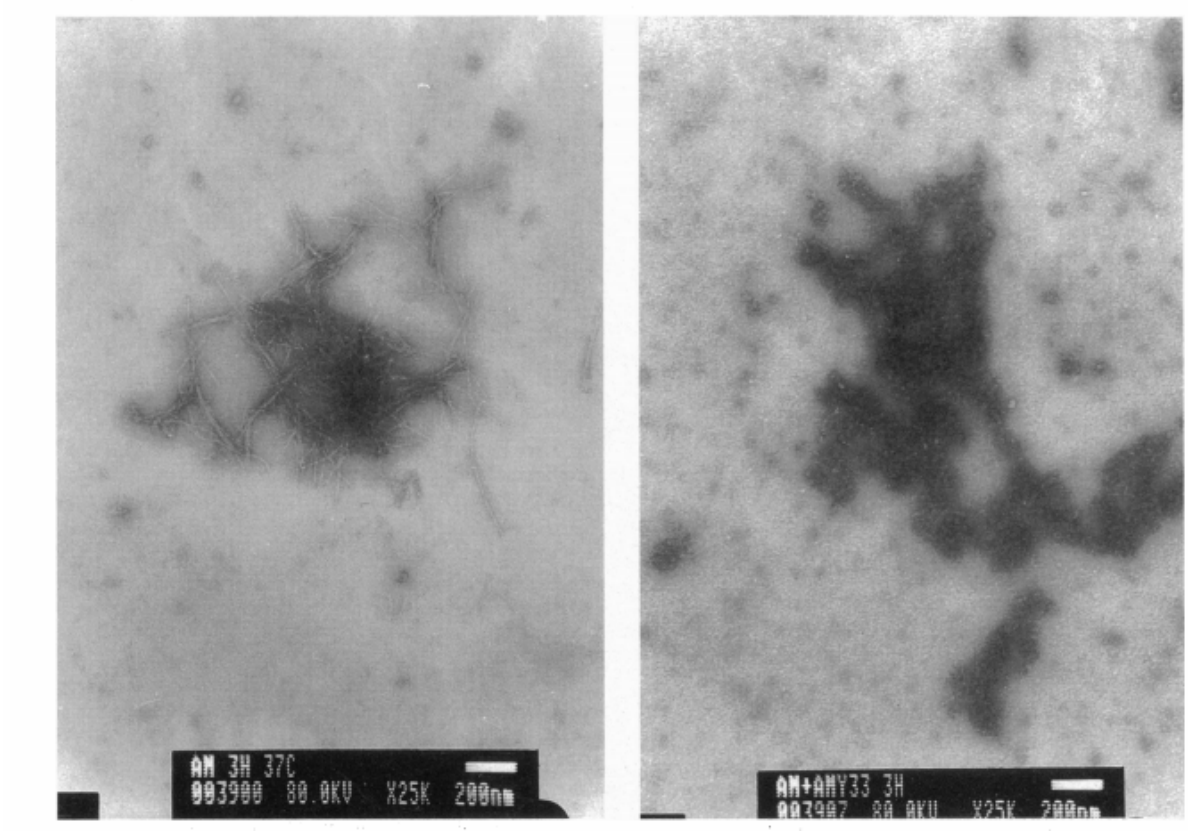

FIGURE 6: Comparison of plaque before and after mAB-33 treatments. An electron micrograph of beta amyloid in the presence (right) and absence (left) of mAB AMY-33 shows that the presence of the antibody disrupted the aggregation of amyloid plaques, and only allowed for shapeless clusters to form (Solomon et al., 1996).

To summarize, the results of the two experiments supported the theory that amyloid plaques do aggregate in areas of the brain most affected by neurodegeneration in Alzheimer's disease. This was verified by the increases presence of the NAB61 antibody in those brain regions. Furthermore, the amyloid plaques are also most likely responsible for cognitive deficits in Alzheimer's, because once the plaques had been degraded by the monoclonal antibody, mice memory was found to have improved (Lee et al., 2006).

However, the issue with the types of antibodies that were studied in these experiments is that they are highly specific in the types of amyloid beta aggregates they detect, and are therefore only effective in denaturing specific subsets of plaque aggregation that leads to Alzheimer's related cognitive deficits. When the monoclonal antibodies effectively detected the amyloid beta proteins that they were designed to detect, they were in most cases effective in reducing peptide aggregation.

Discussion

The monoclonal antibodies are a promising area of research for Alzheimer's treatment if proven to be safe and effective. So far, experiments have yielded mixed results regarding the efficacy of the monoclonal antibodies because they are so specific to beta amyloid conformation, and they can only detect and neutralize amyloid plaques in certain experimental conditions (Solomon et al., 1996). However, they target the root cause of Alzheimer's, so it is still worth researching further if these antibodies can stop the progression of the disease. Furthermore, if the results finding that monoclonal antibodies may reverse cognitive effects of neurodegeneration are upheld, any potential side effects and associated risks involved in using monoclonal antibodies might be offset. So far, the antibodies have not been found to successfully clear the amyloid pathology, and there have been an array of health risks associated with the use of the antibodies (Lee et al., 2006). Even though the research regarding monoclonal antibodies is still in its early phase, the observation that active antibodies can be targeted to specific beta amyloid compartments makes the use of monoclonal antibodies potentially valuable for gene therapy. Recent success in reducing amyloid deposits in mice brains provides the

foundation to further study the effects of monoclonal antibodies against beta amyloid plaques in human brain tissue.

The monoclonal antibodies are such a promising area of research that some monoclonal antibodies have already gone into clinical trial for humans. Even though the monoclonal antibodies have shown success in mice and laboratory models, the results of clinical trials have been largely disappointing. There have not been any consistent findings showing the antibodies breaking down or eliminating the beta amyloid plaques in humans (Prins & Scheltens, 2013). This could be due to a number of reasons including the antibodies being administered too early or late in the disease process, or antibodies that target the wrong type of beta amyloid proteins being used (Prins & Scheltens, 2013). This could also be because researchers don't yet fully understand which types of amyloid plaques are the cause of cognitive deficits in Alzheimer's so a specific monoclonal antibody that attacks the plaques causing Alzheimer's has yet to be tailored. Future directions for research could involve studying the types of amyloid plaques found in Alzheimer's diseased brains so antibodies that target those specific aggregates can be tested for their ability to effectively reduce cognitive issues related to Alzheimer's disease.

Chapter 3

Alzheimer's Case Study

Patient's Complaint

Genevieve Wilson, a 67 year old Caucasian female, arrived at the clinic accompanied by her adult daughter. Her chief complaint was increased forgetfulness which she attributed to old age. Genevieve's daughter reported that Genevieve is experiencing a gradual loss in memory, with her recent memory being the most impaired. Although her memory loss hasn't been precipitous, Genevieve's daughter fears that her impaired memory is beginning to impact her daily life.

History of Present Illness

Genevieve reports that she has noticed her memory is not as good as it used to be. She says she occasionally misplaces her things only to later find them in peculiar locations around the house. She also states that she often feels confused because she will walk into a room only to realize she can't recall why she had gone to that room in the first place.

Genevieve's daughter asserts that her mother's memory has been noticeably impaired for the past two years, and that her ability to care for herself is beginning to be diminished. Genevieve went from misplacing her keys every so often, to not knowing where most of her personal items are stored despite having been a very organized person her whole life. She also states that her mother often forgets appointments, and needs to be prompted to take her medications. Genevieve's daughter said she had initially assumed the memory decline was a result of the normal aging process, but she began to grow concerned when

her mother started to forget the names of close family members. Genevieve will also promptly forget things like whether she showered or had a meal, and she tends to repeat questions several times after they had been adequately answered. Despite her issues with more recent memory, Genevieve seems to remember things like family events that happened 20-30 years ago clearly.

Genevieve denies a decline in her ability to care for herself. She also denies any changes to her mood including irritability, depression, or heightened aggression. She also denies any changes to her physical health. She does not experience any headaches, issues with her vision, or any noticeable muscle tremors.

Medical History

Past Illness: Genevieve suffered a minor stroke when she was 62 and has been on a regiment of baby aspirin ever since. She suffered no long-term disabilities or issues resulting from the stroke. Additionally, she suffers from osteoarthritis in her knees. Genevieve had chickenpox when she was 5 years old but fully recovered with no residual issues related to the infection.

Past surgeries: Genevieve had an appendectomy in 1959 when she was 11 years old, a rhinoplasty in 1967 when she was 19 years old, and she had liposuction in 1983 when she was 35 years old. Furthermore, both her children were born via caesarian in 1976 and 1980 when she was 28 and 32 respectively.

Current Medication: Genevieve takes an 81 mg aspirin daily to minimize the risk of stroke recurrence. She also takes 650 mg of acetaminophen as necessary to alleviate pain resulting from osteoarthritis.

Allergies: Genevieve has no drug allergies. She is, however, allergic to coconut and reports skin irritation resulting from cosmetics containing menthol.

Immunizations: Genevieve receives the influenza vaccine every year. She has also received all childhood vaccinations as regularly scheduled.

Social and Family History

Genevieve is currently retired and she lives alone in her home in Cape Coral, Florida. She is a widow and her son lives with his family in California, while her daughter lives 45 minutes away. Before she retired, Genevieve was a successful travel writer and has traveled the world. She says she misses working and misses socializing with her peers. She also reports feeling isolated after her husband's death; particularly because her children don't live nearby. She has a family history of hypertension (her dad was hypertensive), arthritis (her mother suffered from osteoarthritis), and skin cancer (her mother had benign basal cell carcinoma). She does not know of any other illnesses that run in the family. She denies any drug or tobacco use, and reports consuming no more than a glass of wine once or twice a week with dinner.

Physical Exam

Vital Signs:

Temperature: 98.6°F taken orally

Blood Pressure: 116/72

Pulse: 80 beats/minute

Respiration: 16 breaths/minute

Height: 5’8”

Weight: 164lbs

BMI: 24.9

General:

Genevieve is a lively older woman who appears to be in good physical health. She seems well nourished, and is alert and cooperative.

Head:

Normocephalic and atraumatic.

Eyes:

PERRLA, EOMI, fundi normal, sclera clear, vision is grossly intact.

Ears:

External auditory canals are clear, tympanic membrane is intact and pearly grey, no inflammation, and hearing is grossly intact.

Nose:

No discharge from nares, no swelling, no nasal flaring.

Neck:

Neck is supple, no tenderness, no stiffness, no inflammation, no masses, lymphadenopathy, or thyromegaly.

Throat:

Pharynx and oral cavity appear normal, teeth and gingiva in good condition, no swelling, no inflammation, no exudate, no petechiae, and no lesions.

Chest:

Breathing appears unencumbered, and chest movement is symmetrical.

Cardiac:

S1 and S2 normal, no S3 and S4, no murmurs, no extra heart sounds, no rubs, heart rate normal, rhythm is regular, no peripheral edema, cyanosis, or pallor. Extremities are warm and blood perfusion is good. Capillary refill is under two seconds, and no carotid bruits.

Lungs:

Clear to auscultation, percussion without rales, no wheezing, or stridor. No diminished breath sounds, rhonchi, or dullness.

Abdomen:

No tenderness, soft and non-distended, bowl sounds present and normal, no masses, no organomegaly, no rebound tenderness

Musculoskeletal:

Adequately aligned spine with full range of motion. Normal gait and muscular development, hips symmetrical with full range of motion, legs are straight and symmetrical.

Back:

Spine exam shows no spinal deformities, spinal muscles symmetrical, no tenderness, no muscle spasms, full range of motion is demonstrated, gait and posture appear normal.

Extremities:

No striking deformities. Fingers and hands appear normal, no clubbing or cyanosis of finger or toes. No edema or varicose veins. No joint inflammation or abnormalities, but mild tenderness in the knees. Peripheral pulses intact. No swelling, crepitus, discoloration, nodules or weakness in any extremities. All joints have normal range of motion.

Neurological: Cranial nerves II-XII are intact, cerebellar function is normal, motor and sensory examination of upper and lower extremities was normal, no gagging, strength and sensation is 5/5 in all extremities and symmetric bilaterally, and reflexes are 2+ throughout and symmetrical bilaterally.

Skin:

No lesions or eruptions, normal texture and turgor, no discoloration, normal body temperature.

Psychiatric:

Mental status examination revealed patient to be alert. She is well groomed and wearing clean clothing, but her appearance is a little disheveled. Patient reports that mood is anxious, but good overall. Affect is congruent with stated mood. Behavior was normal, speech was clear, and she was oriented to person, place, and time. Demonstrated good judgement and reason. No hallucinations or delusions. Memory tests indicated deficiency in recent memory— patient couldn't name the president or recall a list of 3 items. Also had difficulty remembering names of objects. Patient didn't express any suicidal thoughts.

Laboratory and Imaging Findings:

CBC-

RBC count: 5.1x10^12 cells/L	Normal Range: 4-6 x 10^12 cells/L
Hemoglobin: 12.1 g/dL	Normal Range: 12.0-18.0 g/dL
Hematocrit: 37%	Normal Range: 35-50%
MCV: 83 fL.	Normal Range: 80-95 fL
MCH: 28 pg/cell	Normal Range: 27-33pg/cell
MCHC: 34.4 g/dL	Normal Range: 32.0-36.0 g/dL
White Cell Count: 6.9x10^9 cells/L	Normal Range: 4.5-10 x 10^9 cells/L
Neutrophil Count: 47x10^9 cells/L (Absolute)	Normal Range: 2.0-7.0x10^9 cells/L

Neutrophil Count (Relative): 55% Normal Range: 54-62%

Lymphocyte (Absolute): 2.4x10^9 cells/L Normal Range: 1.0-3.0x10^9 cells/L

Lymphocyte (Relative): 26% Normal Range: 25-30%

Monocyte Count: 0.4x10^9 cells/L Normal Range: 0.2–1.0×10^9 cells/L

(Absolute)

Monocyte Count (Relative): 8.1% Normal Range: 0-9%

Eosinophil Count: 0.3x10^9 cells/L Normal Range: 0.02–0.5×10^9 cells/L

(Absolute)

Eosinophil Count (Relative): 1.7% Normal Range: 1-3%

Basophil Count: 0.02x10^9 cells/L Normal Range: 0.02–0.1×10^9 cells/L

(Absolute)

Basophil Count (Relative): 0.9% Normal Range: <1%

Platelet Count: 347x10^9 cells/L Normal Range: 150-400 x 10^9 cells/L

MPV: 10.1 fL. Normal Range: 7.5-11.5 fL

BMP-

Sodium: 138 mmol/L Normal Range: 135-147 mmol/L

Potassium: 4.3 mmol/L Normal Range: 3.5-5 mmol/L

Chloride: 104 mmol/L Normal Range: 100-106 mmol/L

Bicarbonate: 27 mmol/ L	Normal Range: 24-30 mmol/L
BUN: 14 mg/dL	Normal Range: 7-20mg/dL
Creatine: 0.8 mg/dL	Normal Range: 0.7-1.3 mg/dL
Glucose: 4.2 mmol/L	Normal Range: <5.6 mmol/L
Antinuclear Antibody- negative Titer 1:40	Normal Range: negative; Titer 1:40-1:60
Vitamin B12-432 pmol/L	Normal Range: 200-900 pmol/L
Cholesterol- 150 mg/dL	Normal Range: <200 mg/dL
LDL: 90 mg/dL	Normal Range: <130 mg/dL
HDL: 60 mg/dL	Normal Range: 40-60 mg/dL

MRI: MRI of patient shows atrophy in the hippocampus and temporal lobes. No signs of hemorrhage, hydrocephalus, or tumors. No diffusion- weighted abnormalities.

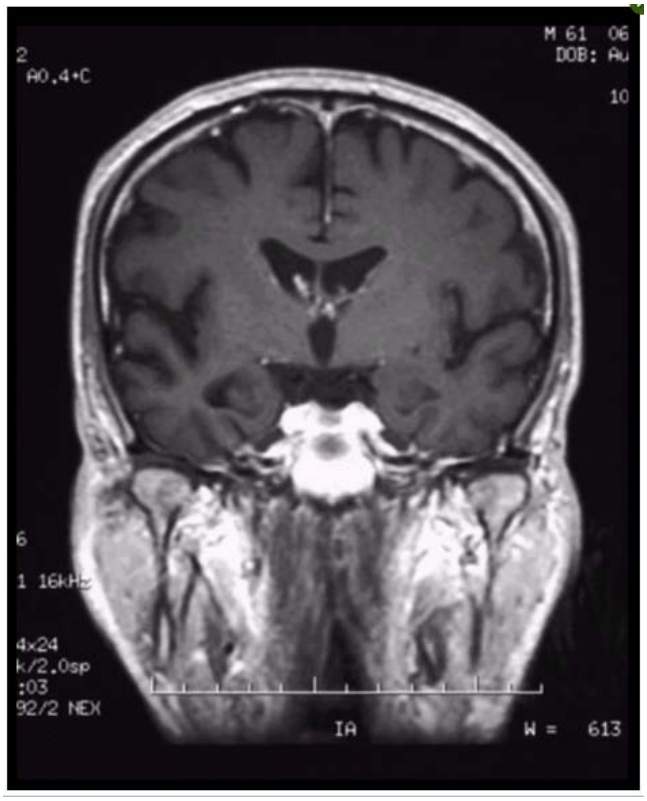

Figure 7: Coronal, T1-weighted MRI scan of patient's brain. Brain image shows hippocampal atrophy located mostly on the right hemisphere of the brain.

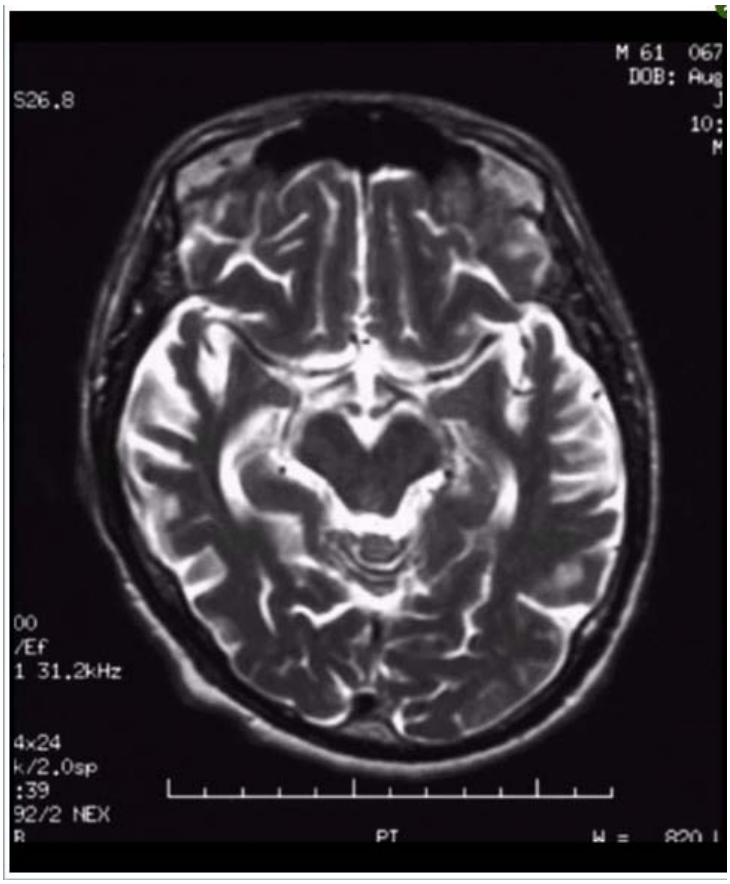

Figure 8: Axial, T2-weighted MRI scan of the patient's brain. Shows atrophy in the temporal lobes.

Cognitive Testing:

Montreal Cognitive Assessment (MOCA) Test: Patient scored 17/30 which is in the low range.

Differential Diagnosis:

Lifestyle factors such as alcohol and drug use where first considered because they are known to negatively impact cognition. It is doubtful that Genevieve's cognitive impairment is due to lifestyle. She denies smoking, illegal drug use, and alcohol abuse.

She is generally in good health, and there is no indication that she is making lifestyle choices that may compromise her cognitive abilities.

Depression was also considered because depression can cause cognitive deficits. However, Genevieve's psychological evaluation did not indicate she was suffering from depression. Neither she, nor her daughter, reported any mood swings, chronic fatigue, or suicidal thoughts. She appeared well nourished and well groomed. Although clinical depression does often lead to a cognitive decline, depression is an unlikely cause of Genevieve's cognitive decline because she isn't presenting with the hallmark signs of clinical depression.

Elderly individuals are prone to falls that can cause a variety of injuries. If a fall results in an injury to the head, the trauma can alter thinking and lead to issues with memory. However, Genevieve did not report any cranial trauma, and a cranial exam during her physical exam revealed her head to be atraumatic and normocephalic. Furthermore, her MRI showed no signs of trauma. Genevieve also denied any recurring headaches or dizziness. She did not display any issues with judgement, or a lack of impulse control. Since she is not presenting with these key symptoms, it is unlikely that Genevieve's neural degeneration and memory issues are a result of chronic traumatic encephalopathy.

Due to the fact that Genevieve had previously suffered from a stroke, multi-infarct dementia was a potential cause for her cognitive impairment. While multi-infarct dementia, which is a result of a number of small undiagnosed strokes, does negatively affect cognitive abilities such as thinking and memory, it is an unlikely to be the cause of Genevieve's memory loss. Her symptoms are inconsistent with multi-infarct dementia

because multi-infarct dementia often presents with periods of sudden decline, rather than the slow progression described by Genevieve and her daughter. Furthermore, there was no evidence of infarction on the MRI, and it is unlikely that Genevieve has suffered another stroke since she is currently on an aspirin regimen, and her cholesterol level was within normal limits. MRI scans did not reveal any evidence of a hemorrhage, hydrocephaly, or a tumor, so those are all unlikely causes of her cognitive decline.

Diagnosis:

Based on the results of the MOCA exam, patient reports of memory loss, and MRI scans showing atrophy in the hippocampus and temporal lobes, it is determined that the cognitive impairment that Genevieve is suffering from is a result of Alzheimer's disease.

Treatment:

There is presently no cure for Alzheimer's disease, but the symptoms can be treated. Genevieve was referred to a neurologist to discuss her options for treatments that help slow the progression of the disease. Since Genevieve is still in the early stages of the disease a good option for her would be Memantine which is a drug that slows the progression of Alzheimer's symptoms for those who have moderate to severe symptoms. She has also been referred to a psychiatrist to help her cope with her diagnosis. This is imperative because many patients diagnosed with Alzheimer's develop depression further perpetuating their cognitive decline. Since Genevieve does not show signs of depression, working with a psychiatrist may result in staving off depression thereby preserving her positive affect and quality of life.

Prognosis:

Alzheimer's can't be cured, but the Memantine should help to slow down the progression of the disease. Unfortunately, even with the medication, her symptoms will continue to worsen over time. As the disease progresses, Genevieve will continue to lose cognitive function, and she will likely lose the ability to care for herself. Her life expectancy will most likely be shortened as a result of this disease.

Plan Implementation/ Follow Up:

Genevieve should make regular appointments to meet with a neurologist and psychiatrist to help manage her Alzheimer's symptoms. As the symptoms worsen, she may be prescribed a cholinesterase inhibitor such as Aricept which may slow down some of the cognitive decline that results from the progression of the disease. However, these drugs may cause sleep disturbances, nausea, and diarrhea. As her cognitive abilities continue to decline, Genevieve may need to move to an assisted living facility to ensure that someone is there to help with daily living tasks if the disease impacts her procedural memory diminishing her ability to independently complete these tasks. At present, Genevieve is probably not ready to enter an assisted living. However, she does need assistance with daily living activities such as making sure she feeds and bathes herself. With her memory being impaired, it is not advisable that she operates her stove and oven. Genevieve's daughter is considering having Genevieve move in with her for additional support in addition to hiring a home health nurse to come and check on her and help her with food and medications when she is at work. Caring for a mother with Alzheimer's disease will likely be very hard on her daughter, so Genevieve's daughter was referred to a support

group to help her cope with the difficulties of being the primary caretaker for a parent with Alzheimer's.

References

Alzheimer's Disease Differential Diagnosis [Internet]. [cited 2015 Apr 23]. Available at: http://emedicine.medscape.com/article/1134817-differential.

Alzheimer's Disease Imaging [Internet] [cited 2015 Apr 14]. Available at: http://emedicine.medscape.com/article/336281-overview.

Blennow, K., de Leon, M. J., & Zetterberg, H. (2006). Alzheimer's disease. *Lancet*, *368*(9533), 387–403. doi:10.1016/S0140-6736(06)69113-7

Chouliaras, L., Rutten, B. P. F., Kenis, G., Peerbooms, O., Visser, P. J., Verhey, F., … van den Hove, D. L. a. (2010). Epigenetic regulation in the pathophysiology of Alzheimer's disease. *Progress in Neurobiology*, *90*(4), 498–510. doi:10.1016/j.pneurobio.2010.01.002

Common Laboratory Values. (2012). (6):247–9.

Förstl, H., & Kurz, a. (1999). Clinical features of Alzheimer's disease. *European Archives of Psychiatry and Clinical Neuroscience*, *249*(6), 288–290. doi:10.1007/s004060050101

Lee, E. B., Leng, L. Z., Zhang, B., Kwong, L., Trojanowski, J. Q., Abel, T., & Lee, V. M.-Y. (2006). Targeting amyloid-beta peptide (Abeta) oligomers by passive immunization with a conformation-selective monoclonal antibody improves learning

and memory in Abeta precursor protein (APP) transgenic mice. *The Journal of Biological Chemistry*, *281*(7), 4292–9. doi:10.1074/jbc.M511018200

Li, X.-L., Hu, N., Tan, M.-S., Yu, J.-T., & Tan, L. (2014). Behavioral and psychological symptoms in Alzheimer's disease. *BioMed Research International*, *2014*, 927804. doi:10.1155/2014/927804

Plains, W., & Lindsay, J. (1994). Environmental risk factors for Alzheimer ' s disease, 1994–1995.

Prins, N. D., & Scheltens, P. (2013). Treating Alzheimer's disease with monoclonal antibodies: current status and outlook for the future. *Alzheimer's Research & Therapy*, *5*(6), 56. doi:10.1186/alzrt220

Reference, H. (2014). Nature Neuroscience., 2–5.

Reitz, C., Brayne, C., & Mayeux, R. (2011). Epidemiology of Alzheimer disease. *Nature Reviews. Neurology*, *7*(3), 137–52. doi:10.1038/nrneurol.2011.2

Solomon, B., Koppel, R., Hanan, E., & Katzav, T. (1996). Monoclonal antibodies inhibit in vitro fibrillar aggregation of the Alzheimer 83-amyloid peptide I1 . I / -, *93*(January), 452–455.