Spring 4-27-2022

Alzheimer's Disease: A Comprehensive Review Including Personal Experience from Retirement Home Patients

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Biology

Submitted in Partial Fulfillment of the
Requirements for the Degree of Bachelor of Science
In the HTC Honors College at
Coastal Carolina University

Spring 2020

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22 April 2022

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Section 1: Introduction

On my first day at work as a caregiver in a memory care retirement home, I felt a variety of emotions. I was nervous and devastated at the hardships I saw, but eager and excited to begin my career in the health field. This job provided me the opportunity to work with the elderly and get my feet in the door with patient care experience. While it is not always the easiest job, it has provided me with so much strength and inspiration to continue to develop a career in health care.

Aging is the decline in abilities or loss of adaptation over time resulting from the process of degeneration (Xia et al., 2018). The changes in abilities are a result of deterioration within the cells and tissues that lead to impairment of essential cellular functions and eventually death (Harman, 2001). Within the aging population, there are about six million Americans, around 65 years and older that are diagnosed with Alzheimer's Disease. This number is expected to grow to 13.8 million by 2060 if a cure is not found. For that reason, Alzheimer's Disease is one of the strongest linked diseases that is age-related ("2021 Alzheimer's disease facts and figures", 2021).

Unfortunately, the number of individuals affected will continue to increase because there is no cure. To be more specific, the number of individuals expected to be diagnosed by 2050 is near 152 million (Breijyeh & Karaman, 2020). From my own personal experience, I have

become familiar with a small group of these six million Americans. From working in a memory care unit at a retirement home for several years now, I have become fascinated with understanding the brain disorder that destroys memory and cognitive abilities slowly over time.

Alzheimer's Disease is a neurodegenerative illness and disease, the most common type of dementia, and the sixth leading cause of death (Sá et al., 2012). The disease was discovered in 1906 and named after Dr. Alois Alzheimer, a psychiatrist and neuropathologist. Over time, a variety of hypotheses have developed regarding the cause behind this multifactorial disease, and these will be disclosed in a later section. Nonetheless, the disease was first observed in changes of the brain tissue of a woman who was said to have die from an unusual mental illness with many abnormal bumps. These bumps are now recognized as tangled bundles of fibers, called neurofibrillary tangles. Additionally, the woman had a massive loss of neurons around the cerebral cortex, a major location site for memories and learning skills (Hippius & Neundörfer, 2003). As symptoms were not understood at this time, she was said to have been at a loss for memory and performing unusual behaviors. My experience in memory care has led me to see the symptoms often vary greatly. These can include trouble finding the right words, impaired judgement, visual or spatial awareness, a decline in thinking abilities, asking the same questions over again, misplacing items, getting lost easily, or even violent lashes that appear in later stages (Kumar et al., 2021). As I have learned in the memory care unit, Alzheimer's can look different for every patient, so the way I approach each patient with care will vary.

AD can occur in two general ways. There are two different onsets to this disease that lie around 60-65 years as the common differential line based off a sociological perspective and randomly used for clinical use, rather than biological importance (Sá et al., 2012). The early

onset form of AD, EOAD, which is extremely rare, results in around 5-10% of cases starting around age 45. If one is diagnosed with early onset there tends to be a more progressive treatment pathway with a shorter survival time period (Ayodele et al., 2021). As far as late onset of AD (LOAD), it remains much more common and can be seen as sporadic, meaning symptoms could be scattered and there may not be any indication of it progressing. Some of the phenotypic differences between the onsets is the rate of progression, metabolic deficiency of the parietal and temporal lobes, division and grade of gray matter atrophy, and the specific allele of the APOE gene, ę4, is associated with the later onset. The significance of gray matter atrophy relies on how strong the reduction in cells are of the brain. In early onset, atrophy will be more spread over a wide area, rather than more localized to a specific area in late onset (Sá et al., 2012).

Section 2: Neuroscience of AD

AD is a disease of the nervous system. The human brain has billions of neurons, specialized cells that function within the nervous system receiving sensory input that are turned into motor output through electrical signals. Alzheimer's disease can either cause a loss of function and death within the neurons, or the opposite with an abnormal accumulation of neurons. In other words, there are two main ways that the nervous system is disrupted by the disease, positive and negative lesions (Breijyeh & Karaman, 2020).

Positive lesions can include any accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, and neuropil threads. The build up of amyloid plaques are extracellular deposits of the beta-amyloid (AB) protein surrounded by amplified axonal endings. The AB protein contributes as a factor causing neurotoxicity and irregular neural function, where it is derived from the amyloid precursor protein located on chromosome 21, which is a familiar link

to Alzheimer disease genetically (Kumar et al., 2021). Therefore, the collection and density of plaques in regions within the brain damages the structures that cause synapses, which is the electrical signal mentioned. The neurofibrillary tangles as a positive lesion are tangled bundles of fiber or abnormal bunches of the tau protein inside the cytoplasm, axons, and dendrites of a neuron that cause a loss of cytoskeletal microtubules (Breijyeh & Karaman, 2020). The function of the tau protein is to stabilize the axonal microtubules (Kumar et al., 2021). If the neuron was healthy, their structure consists of microtubules that function along side the cell body, axon, and dendrites. The tau protein inside these neurons binds to the microtubules allowing them to remain stable. In AD, Alzheimer's affected neurons contain tau proteins sticking together because the microtubules are not able to create that balance with all the chemical changes occurring in the brain (Breijyeh & Karaman, 2020). In early stages, the accumulation of AB starts in the neocortical region and then limbic system, but as the disease progresses the diencephalon, basal forebrain, and cerebellum are affected. On the other hand, tau first affects the entorhinal cortex and hippocampus (Ayodele et al., 2021).

The negative lesions are the losses of brain matter. These negative legions are a large atrophy of neural, neuropil, or synaptic loss. Synaptic destruction within the neocortex results in a loss of memory in the early stages of AD. The losses develop from defects within axonal transport, mitochondria damage, oxidative stress, and any other functions that impact the synaptic sites. With the impairment in function, the loss continues to reduction in dendritic spines, pre-synaptic terminals, and axonal dystrophy. When it comes to diagnosis, these synaptic proteins can become biomarkers for detection of synaptic loss (Breijyeh & Karaman, 2020).

Section 3: Genetics

As an autosomal dominant disorder, Alzheimer's can be completely penetrant when mutations in specific genes are inherited. In fact, 70% of AD cases are developed from genetic factors. This disease is connected to mutations in four major genes, Amyloid precursor protein (APP) on chromosome 21, Presenilin 1 (PSEN1) on chromosome 14, Presenilin 2 (PSEN2) on chromosome 1, and apolioprotein E (ApoE) on chromosome 19 (Kumar et al., 2021).

APP is a transmembrane protein cleaved by a-, B- and y- secretases in order to release AB and is encoded by the APP gene on chromosome 21. The mutations within this gene, which number around 30, cause it to release high amounts of AB that result in accumulation. On the other hand, there is a protective mutant, A673T that decreases secretions of AB, AB40, and AB42, working to protect those from AD. All mutations of AB surround the secretes cleavage site (Breijyeh & Karaman, 2020).

For the PSEN1 and PSEN2 genes, there similarity rate is 67%, with the only variation in the N-terminus and the hydrophilic region. These proteins lead to aggregation of beta-amyloid peptide by disrupting the production of gamma-secretase (Kumar et al., 2021). A mutation in the PSEN2 gene is extremely rare, with around 40 different mutations that have been identified. However, it is more common in PSEN1, with over 200 mutations identified. PSEN1 is a protein that triggers the y-secretase complex and once again plays a factor in AB production from APP. Studies in mice have shown that eliminating this gene can cause synaptic disfunction and memory loss. The mutation is as simple as a single amino acid substitution, but the result is as difficult as loss of memory. A mutation in the PSEN1 gene results in an increase in the ratio of AB42 and AB40 by decreasing only the AB40 level. Contrastingly, PSEN2 mutations are rare

and have little effect on AB production. If there is an effect it is severe on the AB 42/40 ratio and a dramatic increase in y-secretase activity (Breijyeh & Karaman, 2020).

The ApoE gene it is located on chromosome 19 with three alleles that consist of ApoE2, ApoE3, and ApoE4, with again single-nucleotide polymorphisms causing the difference in coding sequences. ApoE is a glycoprotein that mediates cholesterol in the liver and brain of astrocytes and microglia. This ApoE protein acts as a receptor-mediated endocytosis ligand for lipoprotein molecules like cholesterol, while plays a big role in myelin production and normal brain function. Additionally, ApoE has an affinity for the beta-amyloid protein. Out of all the isoforms, ApoE4 has been closely associated with EOAD and LOAD. ApoE2 and ApoE3 serve as a lower risk and even a protective effect (Breijyeh & Karaman, 2020). If only one APOEe4 allele is present then the chances of accumulating the disease are nearly 50%, compared to the average of 90% with two alleles. Each allele lowers the age disease onset and contributes to the AB deposition as senile plaques (Kumar et a., 2021).

Section 4: Different Hypotheses behind Alzheimers

As Alzheimer's Disease is a very complex illness, there are several hypotheses that explain the possible causes behind this disease. While there is still a lot of information that is unknown, these hypotheses include the AB cascade or amyloid hypothesis, the tau protein hypothesis, the inflammation hypothesis, the cholinergic hypothesis, and the glucose hypo-metabolism hypothesis (Du et al., 2018).

The amyloid hypothesis proposes that the abnormal deposition of B-sheets in the central nervous system is the cause of AD. This hypothesis serves as the most recognized and has been the primary reasoning for AD over 25 years now. In patients with AD, the metabolic ability to

break down AB is decreased so the peptides accumulate. AB 40 and AB 42 are important elements to this AB peptide, which represent the number of amino acid residues. Therefore, when AB 42 is building up, amyloid fibrils begin to turn into senile plaques, which we know will contribute to neurotoxicity. Going along with that, the APP gene on chromosome 21 can carry different genetic mutations of APP, which supports this amyloid hypothesis. Mutants in the APP genes lie near B-secretase or y-secretase cleavage sites, which correlates with the increase in AB 42. However, the amyloid process still brings problems to the table that do not seem to run parallel with what it is claiming. When investigating this hypothesis, genetically modified mice were used to look into the effect of AB being deposited in the brain. In the results, senile plaques were found, but the accumulation of tau protein and nerve cell death had not been seen. Therefore, the problem with this hypothesis is the idea that AB fibrils are not truly toxic, nor do they elicit a strong effect on the tau accumulation (Kametani & Hasegawa, 2018).

Moving on, the tau hypothesis holds significance in regard to neurofibrillary tangles, which are composed of the tau protein. Tau is a protein involved with microtubules that are behaving as scaffolding proteins in axons (Du et al., 2018). As tau builds up in these tangles, the accumulation leads to impairing the axons of the neurons. Since a problem was realized within the AB hypothesis, the tau hypothesis continues to draw more attention to the option of therapeutic treatments and studies of biomarkers. Going off this hypothesis with a treatment approach, attempts can consists of blocking of tau aggregation, tau vaccinations, stabilizing microtubules, or control of the kinases and phosphates that have a role on tau function (Kametani & Hasegawa, 2018).

For the inflammation hypothesis, it is proposed that the microglia plays a role in the pathogenesis of AD. Microglia are immune cells of the central nervous system that are associated with brain infections and inflammation, and the first cells to respond when something goes wrong in the brain. Microglia and astrocytes border the amyloid plaques, as they also release pro-inflammatory cytokines (Du et al., 2018). The natural process of synaptic pruning is also caused by microglia, where the brain eliminates extra synapses. Therefore, there is evidence to show that the pruning may get out of control, which results in the extreme loss of synapses and reduced cognitive function (Cepelewicz, 2016). The action of microglia have been found to be a sign in a very early stage of the disease. Non-steroid anti-inflammatory drugs (NSAIDs) were experimented with, but shown to have no impact. With that being said, there is now a high demand on the need for new biomarkers to assess the function of microglial, in order to further analyze this hypothesis (Du et al., 2018).

For the cholinergic hypothesis, the concept lies behind acetylcholine, an important neurotransmitter involved with cholinergic neurons that influence attention span, learning, memory, sleep, and other sensory information. Since cholinergic neurons were thought to be damaged, the hypothesis was suggested a role for cholinesterase inhibitors in the development of AD. The first anti-AD drug, Tacrine, a cholinesterase inhibitor, became available in clinics, until it was shortly taken down with extreme side effects. Inhibiting cholinesterase only eliminates some symptoms, but it provides patients with a hope for the future as it slows progression (Du et al., 2018).

As another early pathogenic concept, there are abnormal metabolic changes that revolve around the glucose hypo-metabolism hypothesis. Glucose metabolism and ATP formation in the

brain is found to be reduced in the cerebral cortex. To determine the abnormality in glucose metabolism, a Positron Emission Tomography (PET) scan can be taken to see this progression. The glucose hypothesis connects with that of the AB cascade hypothesis because when glycolysis is reduced in the brain, the decrease in glucose-dependent functions may result in the build up of AB deposition in those areas (Patil et al., 2012).

Section 5: Diagnostic Abilities

In regards to the diagnostic process for AD, pathological changes can be identified years before symptoms arise. Not only that, but diagnostic abilities have improved with advances in technology to examine the molecular aspects with imaging and recognition of biomarkers. As always, the main exam is the observance of cognitive abilities within the patient and a possible informer, knowledgable of that person. From a personal point of view, I have seen cognitive traits change within patients specifically during the time period of COVID-19 when they were not able to exercise their brain as much without group activities being put into place. Regardless, supportive evidence from several other biological tests are still accompanied for reassurance.

Aside from the recognition of change within cognitive abilities, checking the levels of vitamin B12 and folate can inform us of the disease progression. It has been found that a specific marker with vitamin B12 deficiency has led to the increase in homocysteine levels, which results in brain damage by oxidative stress, a surge of calcium, and apoptosis. In order to check these levels, the serum of vitamin B12 and homocysteine levels can be measured, with a blood count as well (Breijyeh & Karaman, 2020). Within the technology field, imaging methods such as a Magnetic Resonance Imagining (MRI) can be used to make sure the cognitive impairment is not a result of any structural abnormalities, along with looking for atrophy in specific lobes of the

brain. Atrophy in the medial temporal, entorhinal and perirhinal cortex, and the hippocampus can be a key sign for the disease early along. An MRI has the power to evaluate the hippocampal volume and predict other volumes that develop from neuronal numbers (Oostveen & Lange, 2021). After such imaging, abnormality in Cerebrospinal fluid (CSF) biomarkers like low concentrations of AB, increased t-tau or p-tau concentrations, or all can be examined to determine their effect. CSF total tau (t-tau) is a general marker for neurodegeneration, while phosphorylated tau (p-tau) serves as a more specific character for AD because neurofibrillary tangles are often in an abnormal hyper-phosphorylated state (Wattmo et al., 2020). Another approach to take would be the analyzing of metabolic patterns like hypo-metabolism of glucose in the lobes with a PET scan. A PET, Positron Emission Tomography, is a scan used to measure concentrations of molecules in the brain, specifically an abnormal build up. To obtain another perspective, there is also the examining of autosomal dominant family genetic mutations on chromosomes 21 (APP), 14 (PSI), and 1 (PS2) (Kumar et al., 2021).

With all the diagnostic techniques available, there is a division of three clinal stages that help assist the diagnostic process. The first stage, the preclinical stage, marks the pathologic brain changes, and as mentioned previously can start happening up to years before symptoms persist. Within this stage, biomarkers of AD can be detected, but are difficult to predict whether or not it will cause the disease. Following the preclinical stage, Mild Cognitive Impairment (MCI) takes place exemplifying the memory symptoms that are unusual for ones age, but the patient still remains independent. The final stage results in the actual disease, Alzheimer's dementia, where symptoms are now affecting every day activities and their ability to function on their own (Kumar et al., 2021). While working in the retirement home for over 4 years now, I

was able to monitor these stages within a few patients by seeing them switch from the residential independent side to memory care as their cognitive abilities began to take a toll on their health. For some, it may happen quickly, but for others it can slowly progress to the point where a diagnosis or decision is made for their safety and health.

Section 6: Medicine/Treatment

There is no cure available for AD, but there are a variety of treatment options that help manage the symptoms and progression of the disease. To this day, extensive research continues to be conducted in search of the cure. As of now, there are three cholinesterase inhibitors and memantine available to treat the neurotransmitter destruction. In addition, there is an abundance of therapeutic agents and stem cell therapies that may also play a role in the treatment plan. The FDA-approved AD cholinesterase inhibitors are currently donepezil, galantamine, and rivastigmine, followed by the N-methyl-D aspartate (NMDA) antagonist memantine. The inhibitors work by increasing acetylcholine availability, which restrains its breakdown in synapse. However, this method of treatment requires caution in individuals with heart problems because acetylcholinesterase inhibitors (ACHEis) can cause brady-arrhythmias. Memantine is another possible pathway for symptomatic treatment that works to decrease glutamate excitatory neurotoxicity without influencing any physiological actions. This approach words best for those with moderate to severe AD, or together with an ACHEis. Along side the use of these drugs, it is also important to still treat other mental illnesses within the patient that may be adding to the overall state of mind. Therefore, depression and anxiety medicine should still be used as needed since a majority of AD patients are experiencing these illnesses as well. Similarly, antipsychotics can also be administered in the later stages when the patient may become more aggressive or

agitated (Lane et al., 2018). From a more general outlook, keeping AD patients in a regular schedule, challenging the memory they have left, encouraging socialization, and physical exercise programs helps maintain their wellbeing during this hardship. During my time at home in the COVID-19 quarantine period, I was able to continuing working in the retirement home, which allowed me to get a better perspective on the day to day concepts that can benefit the human brain.

Section 7: Conclusion

All in All, Alzheimers can be very detrimental to not only the patient, but the family and friends in their life. As cognitive abilities progressively get worse, daily life of the patient becomes difficult. In the retirement home, my mornings were spent waking up the patients and taking them through a morning routine that allowed them to be ready for the day. When a patient wakes up and they are unable to tell you where they are and what they do to get ready, it creates a devastating impact on the caregiver. For that reason, I have chose to study this disease to learn more of how I can help and what I can do to make daily life easier for those who are suffering. Not only that, but I was eager to learn more about why science has yet to find a cure and what area is lacking in knowledge and research. While this comprehensive review covers only the general concepts, there is a wide variety of information left to be investigated. As I continue my career path into the field of health and medicine, I will fight for those struggling with this disease and provide support to all my patients.

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