Alzheimer's Disease: A Battle Against a Degenerating Brain

Abstract

Alzheimer's disease is a neuro-degenerative disease that causes deficits in memory, thinking and behavior. It is the most common form of dementia, a general term for substantial memory loss and overall decreased cognitive function. Alzheimer's accounts for 60 to 80 percent of all dementia cases (*National Institute of Health*). Although the causes of the disease are not yet fully understood, the effects of the disease are clear: it damages and kills brain cells, while also decreasing the connections between surviving brain cells. As a result, the brain shrinks considerably. Two indications of the disease are plaques and tangles. Plaques interfere with cell-to-cell communication, preventing adjacent cells from exchanging information with one another. Tangles occur when proteins that transport and carry nutrients to brain cells become twisted. This is strongly believed to be the cause of cell death as a result of Alzheimer's, but this conclusion is not definitive and more research needs to be done. Alzheimer's affects more than 5.3 million Americans every year and this number has been on the rise in the past decade (*National Institute of Health*). To invert this trend, research must continue to be promoted in order to find the cause and proper treatments for this debilitating disease.

Introduction

Alzheimer's disease fits into the broader category of neurological diseases that affect the brain, spine and nerves that connect them. The specific cause of Alzheimer's disease is not known, but rather is associated with a complex set of factors like genes, age, and a person's risk for vascular diseases. Doctors are making progress in understanding and diagnosing the disease due to more than $480 million donated to research each year (*Alzheimer's Association*). Our brain changes as we age, just like the rest of our body. Most individuals experience slowed cognitive ability and trouble remembering things as they age; However, signs that brain cells

are failing include major memory loss, constant confusion, and significant changes in how the brain functions.

These symptoms become more severe over time and point to larger issues that are occurring in one's brain; such as Alzheimer's disease.

History, Symptoms and Stages

The first case of Alzheimer's was identified in 1901 by German psychiatrist Alois Alzheimer. The doctor followed the case until she died in 1906. In the five years that followed, eleven more cases of the disease were documented in medical literature, with some of them already using the term "Alzheimer's disease." Throughout the 20th century, an Alzheimer's disease diagnosis was only given to individuals age 45 to 65 who had developed symptoms of dementia. A conference on AD in 1977 led to the frequent diagnosis of Alzheimer's independent of age. For patients older than 65 who had the condition, the term *senile dementia of the Alzheimer type* was used, while classical Alzheimer's disease was used for those younger. Eventually, the term Alzheimer's disease was adopted to diagnose individuals of all ages who showed signs of the disease.

The first stage of Alzheimer's disease is the pre-dementia phase. The symptoms of this stage are often mis-associated with aging and stress. Most notably, deteriorated short-term memory is a key indicator of neurological deficits. This is exhibited as difficulty remembering recently learned facts and inability to retain new information. It can also manifest itself in several more ways such as repeating statements and questions over and over again, not noticing that the question has already been asked before, or misplacing objects in illogical places

such as an iron in a freezer. Impairments in abstract thinking is another symptom associated with this stage of Alzheimer's. This refers to one's ability to solve problems and draw conclusions from presented information. For example, it may be difficult to balance a checkbook because a patient has forgotten what to do with numbers.

The second stage of Alzheimer's disease is the early stage. Increasing impairment with memory and learning leads to a definitive diagnosis at this stage. For a small percentage, more prominent than memory loss is difficulty with language, perception, or execution of movements. Language problems emerge from decreased vocabulary and fluency. However, these deficiencies do not prevent a patient from communicating basic ideas competently. All memories are not affected equally as the disease progresses. New facts are more diminished than episodic memories. These memories are autobiographical in nature, often dealing with times, places and associated emotions. Episodic memories allow one to figuratively travel back in time to a particular event in one's life. Two other types of memory that are less diminished over time compared to new facts are semantic and implicit memory. Semantic memory refers to general world knowledge that one has accumulated throughout one's lifetime. This knowledge is intertwined in experience and correlates to an individual's culture. However, this is different than episodic. For example, semantic memory may contain information about what a cat is, but episodic memory may contain a specific memory about petting a particular cat. Implicit memory refers to the memory of the body (muscle memory), such as how to use chopsticks to eat. While difficulty performing fine motor functions like writing, drawing, and certain coordinated movements may be present, it often goes unnoticed by patients or their relatives.

The third stage of Alzheimer's disease is the moderate stage. This stage is characterized by progressive deterioration of the brain that eventually cripples independence, leaving patients unable to perform most daily tasks. Inability to recall vocabulary makes speech problems more evident, such as someone referring to a toothbrush as "that thing you put in your mouth." Reading and writing skills are also progressively lost. Complex motor sills deteriorate significantly, increasing the risk of falling. This is especially dangerous because falling is one of the largest causes of injury among adults over 65. Perhaps the most detrimental result of this stage of Alzheimer's is the degrading of long-term memories that were previously intact. This has an increased effect on relatives of the patient because he/she may begin to forget their names.

The prevalence of behavioral changes is also indicative of moderate Alzheimer's. This can be indicated by wandering, irritability, aggression, and resistance to assistance or caregiving. Mood swings and personality changes also afflict Alzheimer's patients. Two behavioral phenomena that occur at this stage are the labile effect and sundowning. The labile affect, also known as emotional incontinence, is a secondary neurological disorder defined by involuntary crying, or other uncontrollable emotional displays. These episodes are especially strange because they may be mood-discordant; a patient may laugh uncontrollably when frustrated or mad. Sundowning refers to increased confusion or restlessness in the evening around when the sun is setting. There is no explanation for why this occurs, and 1/3 of Alzheimer's patients will experience some sort of sundowning confusion. The culmination of all these problems may lead to families moving patients from home care to more long-term care facilities.

The last stage of Alzheimer's disease is the advanced stage. During this stage, the patient is completely dependent upon others. Language constitutes simple phrases or even single words, until eventually all language is lost. Most patients can comprehend and reciprocate emotional signals, even despite loss of verbal language skills. Aggressiveness cedes its pervasiveness to apathy and exhaustion. Patients eventually become bedridden and unable to feed themselves due to loss of muscle mass and deterioration of mobility. Death is eventually caused by some external factor, such as ulcer infections or pneumonia, not the disease itself.

Causes and Diagnosis

According to the Mayo Clinic, the cause for 95% to 99% of all Alzheimer's cases is still unknown. The exceptions occur where genetic differences have been identified. However, there are four promising hypotheses for the origin of this disease. The first is genetics. Genetic mutations to protein producing molecules may alter how proteins are transcribed. This leads to the over or underproduction of certain proteins such as Aβ42 and Aβ40. An imbalance occurs between organic material in one's body, which can lead to the degradation of nerve cells. Despite this, most Alzheimer's disease cases can be classified as sporadic, in which genetic and environmental differences act as risk factors. Risk genes increase the likelihood of developing a disease, but do not guarantee it will come to fruition. Several genes have been identified by researchers that increase the risk of Alzheimer's. Apolipoprotein E-e4 (APOE4), discovered in 1993, was the first gene variation found to increase the risk of the disease. Subsequent proteins that were discovered and linked to Alzheimer's include Presenilin-2, Presenilin-1, Amyloid precursor protein.

The cholinergic hypothesis is the oldest educated guess for the cause of Alzheimer's disease. Because of this, most available drug treatments for the disease are based on this hypothesis. It proposes that AD is caused by decreased synthesis of acetylcholine in the hippocampus and frontal cortex, a neural transmitter that is released by nerve cells to communicate with other cells. This hypothesis is substantiated by low cholinergic neuron levels in the nucleus basalis, a region in the basal forebrain that is theorized to function as a regulator of the reality and

virtual reality components of visual perception. Based on this hypothesis, drugs were created to increase the levels of acetylcholine in the brain. Yet, this hypothesis has lost widespread support due to the ineffectiveness of cholinergic neuron proliferating drugs.

The amyloid hypothesis theorizes that clumps of beta-amyloid proteins (A_β) are the main culprit of the disease. The deposits interfere with cell-to-cell communication because A_β accumulation between neurons destroys synapses, which induces neuron loss. This hypothesis is heavily supported by gene mapping research that has been conducted. In a paper found in the *US National Library of Medicine*, researchers sequenced and mapped a precursor gene of A_β to chromosome 21. This was compelling due to the fact that individuals with trisomy 21 (Down Syndrome) fit the neuropathological criteria for the disease by age 40. Such individuals would have a triple copy of amyloid precursor proteins, thus resulting in three times as much A_β as a normal individual. Since A_β is the main component in AD plaques, it is presumed that excess A_β is the cause of the disease.

Genetically modified mice have also provided insights into the amyloid hypothesis. Mice that were injected with a mutant gene that expresses A_β have developed amyloid plaques between neurons in their brain. As a result, they displayed Alzheimer's-like brain pathology and deficits in spatial learning.

The Tau hypothesis states that Alzheimer's disease may originate from tangles induced by tau proteins. Tau proteins are proteins that stabilize microtubules in neurons and thus serve a significant role. Microtubules are part of the structural network (cytoskeleton) within a cell's cytoplasm. They provide mechanical support, cytoplasm organization, and a means of transport. Tau protein abnormalities lead to AD in cases in which the protein is no longer able to stabilize the cytoskeletons of nerve cells. Eventually, neurofibrillary tangles inside the

nerve cell form. This leads to the disintegration of the cytoskeleton, which collapses the cell's transport system. With no transport system within the cell, biochemical communication between neurons is not able to occur, leading to cell death.

Mechanism for Alzheimer's disease

Loss of neurons and synaptic activity in the brain is a key characteristic of Alzheimer's disease. Studies that utilized magnetic resonance imaging (MRI) and positron emission topography (PET) scans have shown decreases in size of specific areas of the brain in people who have Alzheimer's disease compared to similar scans of healthy adults. This disease has been identified as the protein mis-folding disease. The irregular folding is due to plaque accumulation, as previously mentioned. These plaques consist of small peptides of A_β protein that are approximately 40 amino acids in length. A_β is only a fragment of the larger amyloid precursor protein (APP). This protein is essential to neuron growth, post-injury repair, and survival. In Alzheimer's disease, enzymes break up APP into smaller fragments. These fragments are responsible for the plaques that accumulate outside of neuron cells.

An alternative mechanism for this disease also relates to amyloid-beta proteins. The accumulation of these proteins disrupts calcium ion homeostasis. Increased levels of amyloid-beta proteins put oxidative stress on neurons, leaving them susceptible to apoptosis, or programmed cell death. Calcium ions dictate a cell's life from its origin at fertilization to its own programmed death. It acts as a messenger inside the cell, interacting with plasma membrane receptors to initiate intracellular signaling pathways. The most distinctive property of Ca+ ions

is their dual nature: while they are essential to the survival of the cell, they also can initiate cell distress or even cell death. As one can see, the importance of calcium ion homeostasis is evident.