Alzheimer's Disease – The Past, the Present and the Future

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Abstract: Alzheimer's disease (hereafter: AD) is an irreversible, slowly progressive disease of the brain, most often categorized under the umbrella term 'neurodegeneration'. It is said to be a progressive disease in a sense that the symptoms associated with AD, the most common one being difficulty in remembering recent events, kick in steadily with the symptoms getting worse as time goes on, leading to the demise of affected person as they eventually lose their bodily functions. Other symptoms associated with AD include language problems, mood swings and disorientation. This report seeks to address the history, current as well as the future state of AD by taking into consideration the probable causes and preventive mechanisms together with the treatment methods.

Keywords: Alzheimer's Disease, Neurodegeneration, Causes, Preventive Mechanism, Treatment Methods, Mood Swings, Disorientation

1. Introduction

AD is the most common cause of dementia (usually 70-80% of all dementia cases) which usually affects people in their mid sixties. Statistics in 2015 indicated that the number of people with dementia related cases was about 47.47 million. AD and other dementia related cases are thought to be more prevalent in Europe with the Asian and African continent being the least common. However the cases in Asia and Africa seem to be on the rise when recent figures were compared to those compiled in 2009 (i.e. there was an increase of fourfold in both continents). In the United States of America (hereafter: USA), the present number of people believed to have AD stands at 5.4 million. Those at or over the ages of 65 are presumed to be 5.2 million. More so, it is estimated that in the USA, 37 percent of people over the ages of 87 have AD, between the ages of 75 and 84 is 44 percent, 15 percent corresponds to those within the 65 to 74 age group with 4 percent of the people who have AD below the age of 65 [1, 24, 86]. In the United Kingdom, more than 50 percent of all dementia sufferers have AD, the number postulated to be more than 520,000 people [82]. It is presently the sixth leading cause of death in the USA and the fifth of people at

or over the age of 65, killing about 72,914 people in 2006 and 84,767 in 2013 [1, 7, 86]. Some scientists do consider AD to be one of the greatest medical mysteries, and still is, for the fact being that, the pathophysiological concept as well as the diagnostic paradigm in relation to the disease has not been well understood. In other words, the pathogenesis of AD is intricate and as such is difficult to pinpoint to an unambiguous biomarkers, this making AS diagnosis very challenging. In view of this, the difficult treatment methods currently available are inefficacious, though expensive. All these challenges compounded pose a great problem not only to the family of affected people and the society but also in the field of epidemiology [85–86].

Usually, AD is confused with dementia. Whereas AD is a disease, dementia on the other hand is not a disease. Dementia generally is an umbrella word for a group of symptoms, the most eminent ones being impaired memory and thinking, that interferes with a person's ability to do normal things which they were previously able to do without any difficulty such as eating. Take a patient with swollen legs and feet for instance. Clearly one can see the bulging of the legs and feet. Now swelling arises as a result of a build up of fluids. The build up of these fluids can be linked to several

causes such as medications, allergic reactions, blood clot, pregnancy or even poor nutrition [3]. In the same manner, a person who has dementia does exhibit symptoms indicating there is something wrong with their brain, but the particular cause of those changes happening in their brain is unknown.

Another major difference between AD and dementia is that AD, as stated earlier on, is irreversible, however some forms of dementia such as thyroid conditions, vitamin deficiencies and drug interactions are actually reversible, leading to an affected person regaining their normal functions when the problems are identified and treated. Other common causes of dementia are Huntington's disease, Parkinson's disease, Wernicke-Korsakoff Syndrome, Creutzfeldt-Jakob disease and Normal Pressure Hydrocephalus [4–5].
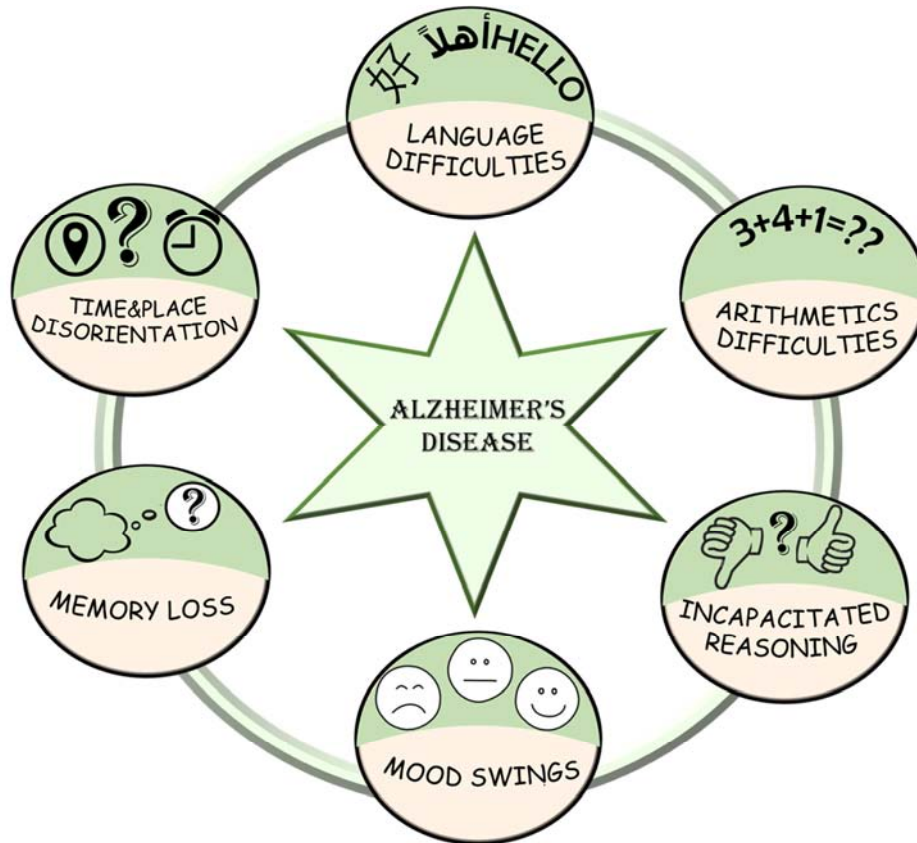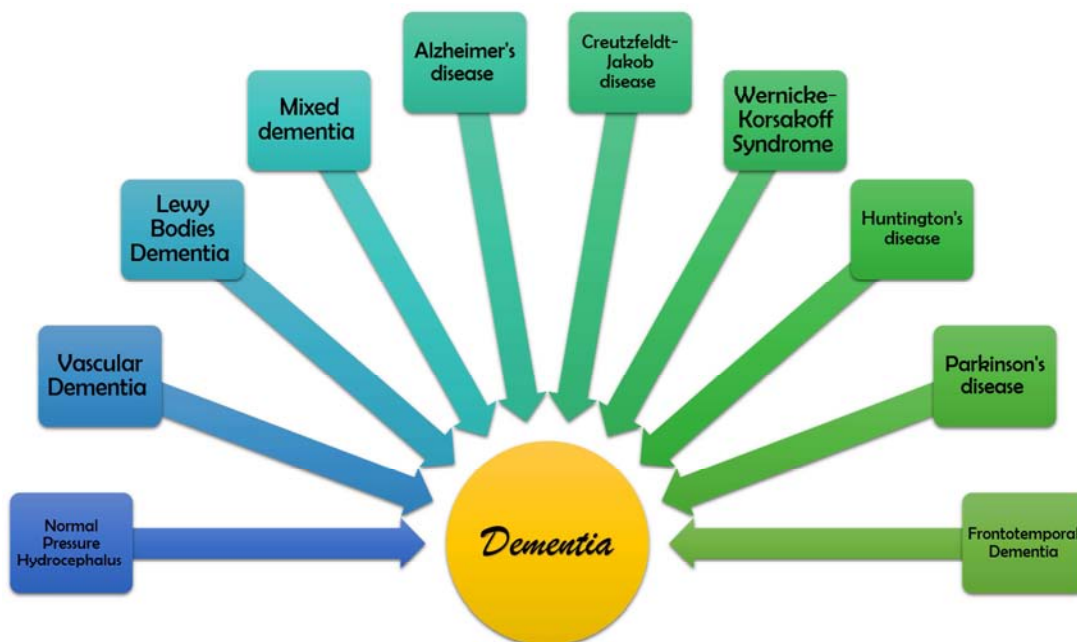

Figure 1. *Some symptoms associated with AD.*

Figure 2. *Pictorial representation of the other forms of dementia.*

Mixed dementia has to do with when an affected dementia individual has more than one type of the different forms of dementia. It can be AD and Down's Syndrome or Vascular dementia and Lewy bodies dementia. However, the most common mixed dementia is thought to be AD and Vascular dementia. Vascular dementia has to do with the hindrance of oxygen and vital nutrients to the brain cells due to an obstruction in the blood flow to the brain cells, thereby leading to deterioration in the thinking skills of the affected person. As there is more than one disease at play in mixed dementia, the symptoms associated are also heterogeneous. It is estimated that about 10 percent of affected dementia individuals have mixed dementia [82–83].

There are variations with regards to the life expectancy following the diagnosis of AD. This can be between 3 and 10 years, depending on the age of the patient. Patients at the age of 80 or older die within 3 to 4 years following diagnosis. Younger patients can however live up to 10 years or even more after they have been diagnosed with the disease [6].

AD can be categorized into two forms based on the commencement of symptoms: Early onset Alzheimer's and Late onset Alzheimer's. Early onset Alzheimer's has to do with when people under the age of 65, most uncommonly in their 30's and 40's but prevalently in their 50's, begin to show symptoms of AD. About 5 percent of all AD cases in the USA are early onset Alzheimer's. Whilst the cause of early onset is presently unknown, some studies have attributed it to the fact that should a parent develop Alzheimer's at a younger age, then there is a high possibility that the child is likely to develop the early onset Alzheimer's as he or she will inherit the genes from the parent in an autosomal dominant fashion, hence Familial Early Onset Alzheimer's. In addition, the causative genes APP, PSEN1 and PSEN2 have also been connected to early onset Alzheimer's. Mutations in the PSEN1 gene have been found to account for 30 – 70 percent of early onset Alzheimer's. On the other hand, mutations in the PSEN2 gene have been found to make up less than 5 percent of the early onset Alzheimer's with mutations in the APP gene amounting to between 10 and 15 percent of early onset Alzheimer's. The mutations in these three genes instigate the disintegration of APP, which in turn forms the amyloid plaques, a distinctive feature of AD. More so these mutations can be detected through sequence analysis [69–70].

The late onset Alzheimer's is the emergence of AD symptoms in people over the ages of 65. Research papers have linked the gene, APOE-4, on chromosome 19 to late onset Alzheimer's and have been found to account for about 30 percent of the late onset Alzheimer's. The late onset Alzheimer's, unlike the early onset Alzheimer's, has no ties to family history and as such no scientific paper has postulated the fact that an inherited genetic material from parent has led to the cause of it. Interestingly, the link of the APOE-4 gene to late onset Alzheimer's has been found to be endemic to the white population. In the non-white population like the Arabs and blacks however, and to the best of our knowledge, there has not been any presently established link between this gene to late onset Alzheimer's [71].

Interestingly, there are individuals who do have AD together with the formation of plaques and tangles but in their case, memory loss happens not to be the preliminary symptom experienced along with the fact that the hippocampal region of the brain is also not the first to be affected. This type is known as the Atypical AD. The atypical AD makes up to about 5 percent of late onset AD with the figure being higher in the early onset AD as it is prevalent, accounting for about one-third of all cases [82].

The three forms of atypical AD are Logopenic aphasia, Frontal variant AD and Posterior cortical atrophy (hereafter: PCA). The logopenic aphasia has to do with the affected individual's speech, both in the process of making as well as understanding, being impeded. This is as a result of the left side of their brain, which deals with language being affected. With the frontal variant AD, the region of the brain affected is the frontal lobe. The frontal lobe helps in the planning and decision making of an individual. As such when affected, these functions are severely compromised [82].

In PCA however, also known as the Benson's Syndrome, an affected individual labor in discerning objects, reading, walking on rough grounds as well as using stairs and escalators along with blurred vision. This is because the affected area of the brain, which is the occipital lobe specifically the Brodmann's area 17, the occipito-parietal cortex and the occipito-temporal cortex, is responsible for the identification and processing of visual images along with spatial awareness. Whereas the occipito-parietal cortex deals with the "where" part in vision, the occipito-temporal handles the "what" part. PCA is deemed to account for 4 percent of all dementia cases and 5 percent of all AD cases [82, 84].

2. Phases of AD

AD on the whole has 7 stages. Stage 1 is the state of no reported impairment or abnormality, be it physical or mental. The individual continues to exhibit normal life behavior, going about their normal daily routine. At this stage, only a PET Scan can detect whether or not the individual has Alzheimer's [26, 72].

Stage 2 is where minimal impairment begins to crop up with a distinct example being forgetfulness. At this stage, the individual fails to recall normal and simple acts such as a word or the whereabouts of objects such as pens, pencils and keys put away not long ago [26, 73].

Then the changes in the individual, such as thinking and reasoning become lucid. At this stage, for example, the individual fails to retain memory of reading done or names of people a moment ago. This is the Mild Cognitive Impairment stage, which is stage 3 and can last anywhere between 3 and 7 years [26, 72]. The number of people over the age of 65 having Mild Cognitive Impairment is estimated to be between 15 and 20 percent. It is postulated that 32 percent of

individuals with Mild Cognitive Impairment develop AD within the space of 5 years [86].

In the stage 4 of the disease, which is the Mild Alzheimer's, the individual's short memory is impeded and as such begins to forget details about themselves as well as the current season. More so their ability to cook meals is hindered together with their inability to carryout simple abstracts such as enumerating backwards from 100 within a space of 7 seconds. Mild Alzheimer's time span is about 2 years [26, 72–73].

Moderate AD, which can last for about anywhere between 1 and 2 years, is stage 5. It is at this stage the individual begins to lose track of time as well as some personal details such as date of birth and contact number. Their clothe choice for the season is also hampered in a sense that they might select summer clothes for winter outing and vice versa. However, their recollection of family member's names as well as their ability to eat, bath and use the toilet is done with ease [26, 73].

With stage 6 of AD, which is Moderately Severe AD, the individual cognitive skills begin to be grievously exacerbated. The individual owing to the fact that they are mostly puzzled about their immediate ambience needs round the clock supervision. Moreover, their ability to use the toilet, bath, recall either personal history or faces is profoundly impaired. Furthermore, individuals at this stage of the disease tend to gallivant repeatedly. There is also the experience of acute changes in behavioral and personality traits such as delusions, paranoia and hallucinations. Moderate Severe AD can last for about 2 and half years [26, 72–73].

Severe dementia is stage 7 of AD. At this stage of the disease, the individual is unable to make conversations on account of the fact that their speech recognition is severely impaired. Individuals are succored with movements, especially eating, walking and sitting together with the motion of the head. Swallowing becomes very difficult for the individual during the latter part of stage 7 [26, 73].

3. The History of AD

The AD was named after the German physician, Dr. Alois Alzheimer, who first detailed the disease in 1906. In Dr. Alzheimer's biography, he was described as being an obsessive caring and dedicated doctor and scientist whose main aim was to find an unimpeachable connection regarding the clinical variations and pathology of a dementia brain examined during autopsy [1]. Prior to Dr. Alzheimer's first reported case, AD was referred to as 'senile dementia' with the description as a state of psychological incompetence. In the late 19th century, the word 'dementia' was perceived as an irreversible disorder of intellectual functions such as memory in the elderly [8].

Dr. Alzheimer's first documented AD patient was a 55-year-old woman by name, Auguste Deter, who had been admitted to the state asylum in Frankfurt. Her symptoms began at the age of 51 and included a rapid decline in memory, paranoid delusions hallucinations and other aggravated psychological changes. During Dr. Alzheimer's first encounter with Auguste Deter, his first question to her was "what are you eating?" At that time Auguste had just finished her lunch that comprised of cauliflower and pork. To the question Dr. Alzheimer's posed, Auguste response was "Spinach". At that moment she began to gnaw the meat and so the follow up question was "what are you eating now?" And Auguste reply was "I eat the potatoes first, followed by the horseradish" [1].

On 2nd April 1906, about four and half years following the onset of the symptoms, Auguste Deter died and her brain was sent to Dr. Alzheimer, who at that time had moved to the Munich Medical School to work with German psychiatrist, Dr. Emil Kraepelin. It was Dr. Emil Kraepelin, who invented the name "Alzheimer's disease" in the eighth edition of his book, Psychiatrie [9]. In order to visualize the presence of neurons, Dr. Alzheimer employed the silver staining technique to perform the autopsy on Auguste Deter's brain. Noble prize winners Camillo Golgi and Santiago Ramon y Cajal designed this technique. Camillo Golgi, an Italian neurologist was the first to design the technique with Santiago Ramon, also a neurologist from Spain, doing the modifications of the technique. It was during the autopsy that he found what was later to be referred to as the amyloid plaques and neurofibrillary tangles and subsequently excogitated that the lesions might either be the cause or the effect of the present AD or probably the combination of both [1, 57].

Ensuing from the first reported and published findings by Dr. Alzheimer, quite a number of developments have taken place. These developments can be categorized into 5 main groups. The 'first discovery' of the disease was between the years 1906 and 1960. The 'modern era' between 1970 and 1979, which is followed by the 'awareness' of the disease in the 1980's. As the disease started getting attention, 'treatments methods' began to crop up. The current era is what is termed as the 'progress and hope' of the disease [11].

3.1. The Discovery Era (1906 – 1960's)

Succeeding the first reported case by Dr. Alois Alzheimer was the invention of the electronic microscope in 1931 by Max Knoll and Ernest Ruska, both Germans. The invention of the electronic microscope allowed scientists to study the brain cells in more detail [11].

Noble prizewinners, Henry Dale and Otto Loewi in 1936 singled out the neurotransmitter, acetylcholine, as having a link to AD. This was the first neurotransmitter to be connected to the disease leading to the birth of the cholinergic hypothesis, which states that the cause of AD is as a result of decreased acetylcholine in the brain [12].

In 1968, the first validated measurement scale for evaluating the cognitive and functional decline in older adults was developed, thereby enabling researchers to find the connection between the level of measured impairment of the brain, the number of brain lesions and the volume of damaged tissues [11].

3.2. The Modern Research Era (1970 – 1979)

This started with the establishment of the National Institute on Aging on 7th October 1974. It is currently the primary federal agency that supports Alzheimer's research. In his editorial published in the Archives of Neurology, Dr. Robert Katzman, a neurologist, pinpointed AD as the most common cause of dementia and poses a big challenge on public health [11]. The tau protein, which is one of the prime suspects in AD, was discovered around this era, specifically in 1975, by American cell biologist, Marc W. Kirschner [59].

3.3. The Awareness Era (1980 – 1989)

Ensuing from the modern research era was the formation of the Alzheimer's Association on 10th April 1980, which had its core objective centered on the care, support and research for AD. The increase in AD awareness led to the designation of National Alzheimer's Disease month on 1st November 1983 [11].

On March 1984, George Glenner and Cai'ne Wong identified the main component of Alzheimer's brain plaques called the beta-amyloid, which also happens to be the chief suspect in causing the nerve cell damage. Twenty-two months later, on 14th January 1986, the tau protein was identified as the key component of tangles in AD. This was the second telltale sign regarding the pathology of the AD and like the beta-amyloid, was also responsible for the nerve cell degeneration. One year later, the first gene associated with AD was singled out. The gene, Amyloid-beta Precursor Protein (APP), was spotted on chromosome 21. The alteration of the APP gene leads to the production of the neurotoxins, amyloid beta peptide, which is suspected to be one of the main causes of AD [11].

7th May 1987 saw the first Alzheimer's drug trial, Tacrine, marketed under the trade name, Cognex, by the Warner-Lambert Pharmaceutical Company. This pharmaceutical company is presently known as Pfizer [11].

3.4. The Emergence of Treatment Era (1990 – 1996)

Following successful clinical trial, Tacrine was approved for use by the Food and Drug Administration (hereafter: FDA) on 24th March 1993. The drug particularly targeted the memory and thinking symptoms associated with the disease. However, it had a dose limiting side effects that included diarrhea, nausea, vomiting, abdominal discomfort, dizziness, headache, anxiety, blurred vision, dry mouth and insomnia. All these side effects were the typical symptoms of cholinergic stimulation. As such, on 24th May 2012 the use of Tacrine was discontinued in USA by virtue of these safety concerns (as it had the potential to damage the liver) coupled with the availability of other acetylcholinesterase inhibitors [11, 13, 14, 15, 68].

Former USA President, Ronald Wilson Reagan on 5th November 1994 disclosed his diagnosis with AD to the public. Prior to his disclosure, the Alzheimer's Disease International, on 21st September 1994 launched the first World Alzheimer's Day [11].

In 1995, the first transgenic mouse model with an Alzheimer's-like brain pathology was developed by inserting it with the APP gene. 1996 saw the second Alzheimer's drug, Donepezil, under the brand name Aricept, approved by FDA, and in 1999 published results showed that plaques and other brain changes associated with AD were inhibited when the transgenic "Alzheimer's" mice was injected with the amyloid, thus the birth of the first successful Alzheimer's vaccination in mice [11].

3.5. The Era of Progress and Hope (2000 – Present)

Between the years 2000 and 2014, the FDA approved five medications for the treatment of AD. These are Rivastigmine (brand name: Exelon, 2000), Galantamine (brand name: Razadyne, 2001), Memantine (brand name: Namenda, 2013), and Donepezil and Memantine (brand name: Namzaric, 2014) [31].

The Alzheimer's Association in partnership with the National Institute on Aging, in 2003, launched a genetic study to collect blood samples from people who had a history of the development of AD later in life in their family. This was done so as to unearth other genes associated with the disease. Various launches have subsequently taken place, including Alzheimer's Disease Neuroimaging Initiative (2004), The Alzheimer's and Dementia Journal (2005), the Healthy Brain Initiative (2008), The Alzheimer's Clinical Database (2010), The Alzheimer's Association Trial Match (2010) and the first major clinical trial for the prevention of Alzheimer's Disease (2012) [11].

In 2013, the International Genomics of Alzheimer's project researchers revealed 20 genetic variations having a correlation with an increased risk for AD. Out of these twenty variations, there were eleven new genetic variations that had not been previously connected to AD [11].

4. The Present State of AD

So what is currently known about AD with regards to the cause and the treatment methods available? The three prominent areas being researched heavily today by scientists have to do with the two chief prime suspects of AD, the tau protein, and the beta amyloid precursor protein, along with the genetic variations associated with the disease.

4.1. The Tau Protein

Every human being has an exuberant amount of tau protein in the neurons of their central nervous system and less common in the oligodendrocytes and astrocytes of the central nervous system [16]. The tau protein is made following the instructions provided by the Microtubule Associated Protein Tau gene located on chromosome 17. The tau protein, predominantly active in the distal portions of the axons, provides stability and flexibility to the microtubules. Microtubules, aside aiding in the maintenance of shape, also play a fundamental role in cell division along with transport of materials within the cell [17, 60].
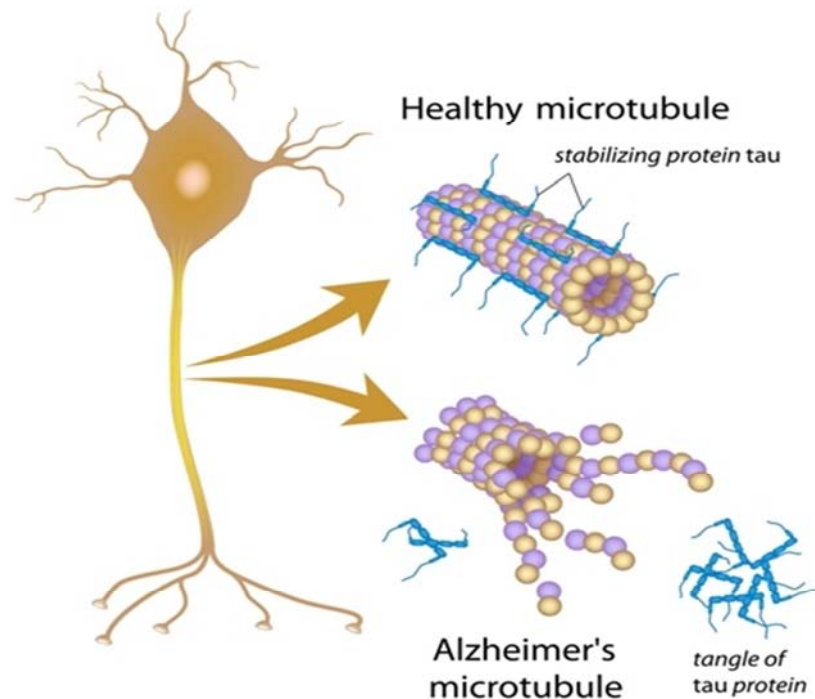
Figure 3. A picture illustrating the difference between a healthy and a diseased neuron. The tau protein in the healthy neuron as seen in the picture is holding the microtubules together, thereby stabilizing them. The opposite is seen in the diseased neuron [66].

The tau protein is able to control the stability of the microtubules through isoforms and phosphorylation.

Generally, the adult brain has 6 tau isoforms, which differ from each other in length from 352 to 441 amino acids as well as by the number of their binding domains. Three of the six isoforms, which are the shortest isoforms in the central nervous system comprise of three repeated sections (i.e. R1, R3, R4) when bound to the microtubule domain, whereas the other three, the longest isoforms consist of four repeated sections (i.e. R1, R2, R3, R4) when bound to the microtubule domain [17, 60].

The tau protein undergoes different kinds of modifications after translation. The prevalent ones are the phosphorylation of serine, threonine and tyrosine. The phosphorylation of tau takes place at 79 sites in the central nervous system. Some of these phosphorylation sites are Thr39, Ser198, Thr205Pro, Ser262, Ser324, Ser352, Ser396Pro, Ser416 and Thr231Pro [131, 132]. The different kinases such as Glycogen Synthase Kinase 3 (GSK-3), Protein Kinase C and Protein Kinase N1, as well as phosphatases such as protein phosphatases 1, 2A and 2B regulate the phosphorylation of tau [131, 20]. Once these kinases are activated, they result in the disruption of the microtubule organization [20]. A couple of research papers have attributed the formation of neurofibrillary tangles being caused by the hyper-phosphorylation of the tau protein [21]. More so, other studies have suggested that the activation of caspases and cleavage of tau in the brain of patients suffering from Alzheimer's disease may proceed to the formation of neurofibrillary tangles [132]. As the disease progresses, there is an aggravation in not only neural loss, but also the number of neurofibrillary tangles [23]. The hyper-phosphorylation of the tau protein has also been connected to peroxynitrites in some cases [21]. This peroxynitrites oxidates the receptors, tyrosine kinase and G-protein coupled, thereby inhibiting the activation of the Glycogen Synthase Kinase 3 enzyme by the protein kinase B and protein kinase C. The enzyme, Glycogen Synthase Kinase 3, quintessentially prevents the hyper-phosphorylation of the tau protein. Interestingly, an examination of an Alzheimer's brain has revealed some form of hyper-phosphorylation of all the six isoforms of the tau protein taken place [58–60]. The hampering of tau dephosphorylation has been associated with hydroxynonenal, a compound that arises from the lipid oxidation of arachidonic acid [133].
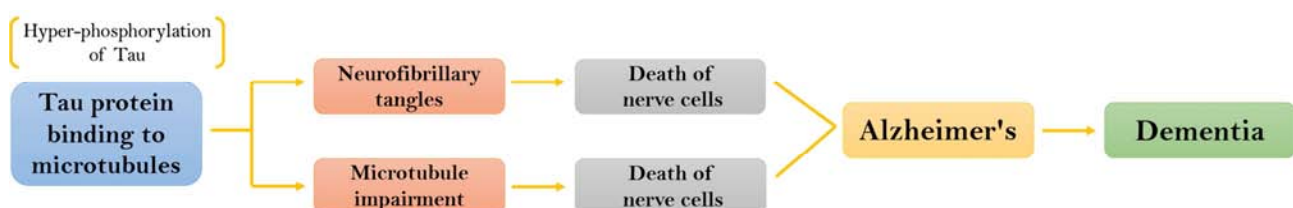

Figure 4. The Tau Protein Hypothesis [60].

4.2. The Amyloid-Beta Precursor Protein

The amyloid-beta precursor protein, found in several tissues and organs such as the brain and the spinal cord, is made following the instructions provided by the APP gene. The APP gene, located on chromosome 21, is one of the 23 pairs of chromosomes found in the human body and also happens to be the smallest human chromosome. Chromosome 21 accounts for about 45 million base pairs, constituting to about 1.5 to 2 percent of the total DNA in the cells. Although the entire crystal structure of APP continues to be elusive, certain domains have been identified in its sequence. The APP has an extracellular section as well as the intracellular section. The extracellular section, which is the larger one between the two, is made up of the E1 and E2 domains along with an acidic domain linking these two domains. In the E1 domain is the growth factor-like domain together with the copper-binding domain. Researchers have elucidated these two domains successfully. Between the acidic and E2 domain lies a protease inhibitor region. There is also the alpha-beta region section within the APP. It is the mutations taking place within this region of the APP gene that has been found to lead to aberrant production of the amyloid-beta theorized to possibly be one of the primary causes of AD and has been found to be responsible for about 10 percent of all early-onset AD. During the mutation of the APP gene, the amino acid Valine in the amyloid precursor protein is replaced with amino acid isoleucine. When that

happens, there is an increased production of the amyloid β peptide. The mutation also leads to the production of a slightly longer and stickier form of the peptide. Upon the amyloid protein being released from the cell, they conglomerate in the brain and eventually form the amyloid plaques. These amyloid plaques lead to the death of the brain cells, which is a characteristic feature of AD. Fascinatingly, there is thought to be a protection mutation, A673T, which also takes place within the APP gene. Albeit, the A673T mutation regarding the toxicity enervation of the amyloid-beta is not apparent, it has however been shown to curtail not only the build-up of the amyloid-beta by 40 percent but also has the tendency to recede the amyloid-beta aggregation in vitro. Should this result be successfully translated into the human brain, it is postulated to result in the reduction of amyloid-beta in individuals having the A673T mutation by 20 percent. In spite of the fact that the main function of the amyloid precursor protein still remains inconclusive, it has been suggested that it might have a role to play in the regulation of neural plasticity and synapse formation as well as impairment of the blood vessel function [10, 19, 32, 90–93]. Protein phosphatase 2A has been reported to result in tau phosphorylation following it being down–regulated by the amyloid beta. Protein phosphatase 2A is one of the phosphatases involved in the regulation of tau phosphorylation [129].
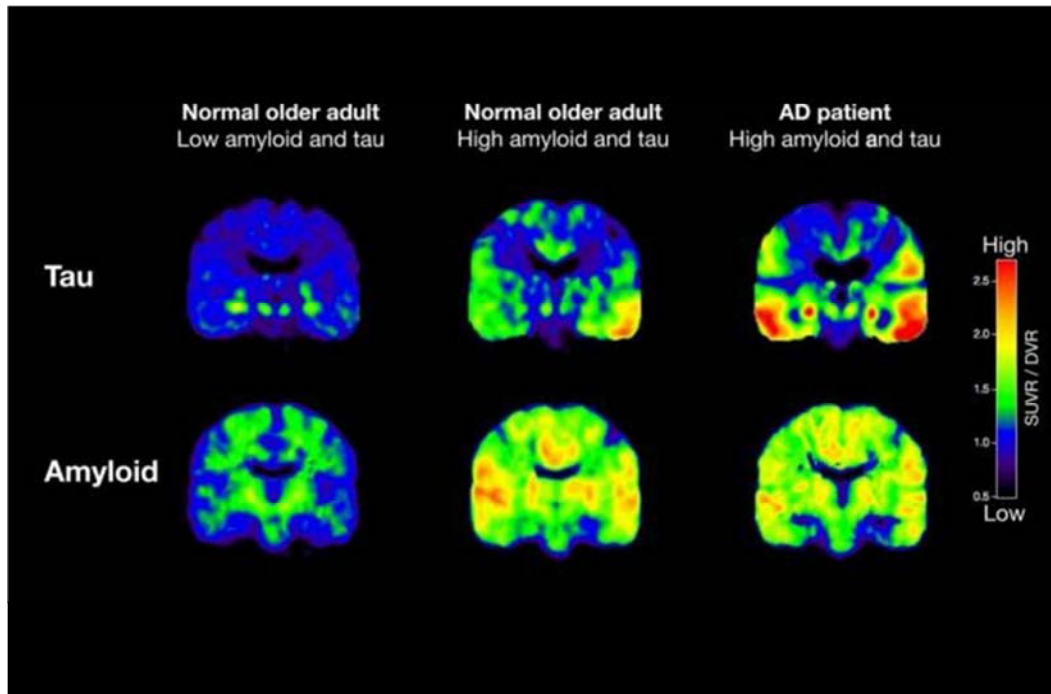

Figure 5. A Positron Emission Tomography scan showing the spread of tau and beta amyloid protein in the brain of three different people: Normal older adult with low amyloid protein and tau, Normal older adult with high amyloid protein and tau and an AD patient with high amyloid and tau. The blue color indicates a low accumulation of amyloid and tau whereas the orange-reddish colour indicates high levels of amyloid and tau accumulation [67]

4.3. The Genetic Variation

The other three genes, bar APP genes, associated with AD are Presenilin 1 gene (hereafter: PSEN1), Presenilin 2 gene (hereafter: PSEN2) and Apolipoprotein E gene (hereafter: APOE) [33].

4.3.1. The PSEN1 Gene

The protein, Presenilin 1, is made following the instructions supplied by the PSEN1 gene. The presenilin 1 protein is a subunit of the gamma secretase complex. Studies show that the gamma secretase complex is responsible for the processing of the Amyloid Precursor Protein. This process involves cutting the Amyloid Precursor Protein into minor peptides, with one prime example being the Soluble Amyloid Precursor Protein. The early-onset AD is associated with the mutation of the PSEN1 gene. The gene mutation of the PSEN1 results in the modulation of the DNA nucleotides of the marked segment of the PSEN1 gene, eventually leading to the aberrant production of the presenilin 1 protein. Subsequently, an erroneous presenilin 1 meddle with the gamma secretase complex function, which further disorders the Amyloid Precursor Protein process, thereby leading to the abnormal production of amyloid plaques in the brain [46].

Fascinatingly, studies have also shown that the absence of the PSEN1 gene has no effect on the cleaving process of alpha and beta secretase of the extracellular domain of APP. However, its absence does prevent the cleavage of the transmembrane domain of APP by gamma secretase. This further leads to the accumulation of carboxyl-terminal fragments of APP. Furthermore, the production of amyloid peptide drops by 5 folds. A mutation in the PSEN1 gene causes an inhibition of PSEN1 activity and is a potential target for anti-amyloidogenic therapy in Alzheimer's disease [109]. The PSEN 1 has also been delineated to trigger phosphoinositide 3–kinase. The triggering of phosphoinositide 3–kinase renders GSK-3 inactive. GSK-3 discussed earlier inhibits hyper tau phosphorylation. In view of this, mutation in PSEN 1 can be surmised to cause neurofibrillary tangles as well as microtubule destabilization [130].

4.3.2. The PSEN2 Gene

Whereas the PSEN1 gene mutation accounts for about 10 percent or less of all early onset AD, the PSEN2 mutation on the other hand accounts for about 5 percent or less of all early onset AD [48]. The PSEN2 gene supplies the information for making presenilin 2 proteins. Presenilin 2 proteins process the proteins that transmit chemical signals necessary for cell growth and maturation. Currently the two mutations of the PSEN2 attributed to AD has to do with the alteration in the amino acids used in making the PSEN2 [47]. The first mutation has to do with amino acid isoleucine displacing the amino acid asparagine whereas the in the second mutation, the amino acid methionine is replaced by amino acid Valine. These two mutations results in the over production of the amyloid beta precursor protein that eventually forms the amyloid plaques in the brain [47].

4.3.3. The APOE Gene

The APOE gene makes the apolipoprotein E protein. This protein together with fat forms the lipoprotein, which is responsible for the removal of cholesterol from the bloodstream, thereby preventing cardiovascular diseases such as heart attack and stroke. The APOE gene comes in three versions, or what scientists call allele. An allele is basically an alternating form of the same gene. The three versions of the APOE gene are APOE-ε2, APOE-ε3 and APOE-ε4 with the APOE-ε3 being the most inherited version by humans. Although the role of APOE-ε4 in connection to AD has not been well understood, studies have suggested about 40 to 80 percent of people with AD carry at least one copy of the APOE-ε4 allele, with those carrying two copies of the APOE-ε4 allele even at a higher risk of developing the disease. Despite the fact that 40-65 percent of patients suffering from Alzheimer's disease have at least one copy of the 3 alleles, the presence of APOE-4 is not determinant of the disease. Conversely, some people who lack APOE-4 genes develop Alzheimer's [94]. Tests for the presence of APOE gene can only predict the amount of risk the patient is at for developing the disease. However test results are not enough for a doctor to make recommendations to a patient to undergo specific treatment for AD [95]. Patients with two APOE-4 alleles are at a risk of up to 20 times to be affected with Alzheimer's.

Among APOE-4 carriers, another gene, GAB2, is thought to further influence the risk of getting AD [96].

There is also evidence that the APOE-2 allele may serve a protective role in AD. At an early age, people with the genotype APOE 4,4 are at the highest risk of developing AD. Although patients with the APOE 3,4 genotype are at an increased risk, they aren't as much as compared to those homozygous for APOE 4. The APOE 3,3 genotype is considered at normal risk for Alzheimer's disease. The genotype APOE 2,3 is considered at less risk for Alzheimer's disease. People with both a copy of the 2 allele and the 4 allele, i.e. APOE 2,4, are at normal risk similar to the APOE 3,3 genotype [97].

The APOE-ε4 allele, likewise the PSEN1 and PSEN2 genes also play a role in the formation of the amyloid plaques in the brain tissues of people affected with the disease [48, 49].

As at 2010, there were 695 genes associated with AD as published on Alzforum. In addition, the strongly related genes, as at April 2011, linked to AD based on their P-value (i.e. statistically significant) were APOE–2, 3,4, BIN1, CLU, ABCA7, CR1, PICALM, MS4A6A, CD33, MS4A4E and CD2AP [2].

Table 1. The frequency of the APOE gene [122].

Allele	Frequency
E2	0.04
E3	0.58
E4	0.38
E2/E2	0.003
E2/E3	0.046
E2/E4	0.026
E3/E3	0.343
E3/E4	0.434
E4/E4	0.148

The high risked genes associated with AD

Gene	Location	Causative/Susceptibility
PSEN1	14q24.2	Causative
PSEN2	1q42.13	Causative
APP	21q21.3	Causative
APOE	19q13.32	Susceptibility
B1N1	2q14.3	Susceptibility
CLU	8p21.1	Susceptibility
ABCA7	19p13.3	Susceptibility
CR1	1q32.2	Susceptibility
PICALM	11q14.2	Susceptibility
MS4A6A	11q12.2	Susceptibility
CD33	19q13.41	Susceptibility
MS4A4E	11q12.2	Susceptibility
CD2AP	6p12.3	Susceptibility

4.4. Environmental Factors Associated with AD

A study in 2004 (Philadelphia) showed that genetics isn't the only cause of Alzheimer's disease. Brenda L. Plassman, PhD, through her studies, showed that identical twins (genetically same) don't both develop Alzheimer's disease at the same time.

The ApoE-4 gene isn't the only gene responsible for Alzheimer's disease. Studies show that APOE-4 alone increased the risk for Alzheimer's disease by a factor of 2.83. When considered along with one's lifestyle and environment, the APOE gene increased the risk by a factor of 11.42 [74].

Air pollution also contributes majorly to the deployment of Alzheimer's disease. Since ultrafine particulate matter can cross the cell membrane, it's spread cannot be blocked by the blood-brain barrier matter has been found in the erythrocytes of the brains of patients suffering from Alzheimer's [75]. People living in highly polluted areas show distortions in their blood brain barriers. This could serve as a risk factor for Alzheimer's disease [76]. Although pollution is one of the major causes of pollution, people prone to pollution carrying the ApoE4 gene may be more susceptible to inflammatory neurodegeneration [77].

Exposure to particulate matter, ozone, diesel exhaust, and manganese triggers the expression of cytokines, which results in oxidative stress in the brain [78]. Microglia in the brain are activated by cytokines, which could cause neurodegeneration. Elevated cytokines trigger the enzyme COX2 in the capillary lining of the brain. This produces a highly inflammatory prostaglandin, PGE2. This prostaglandin stimulates amyloid-beta production [77], forming a bridge between particulate matter and Alzheimer's disease. Polychlorinated biphenyls (hereafter: PCBs) have also been found to hinder normal brain development [79]. The mechanisms by which PCBs may cause neurodegeneration are not well understood. Nonetheless, it been stated that some PCBs interact with the aryl hydrocarbon receptor trigger the activity of certain enzymes that cause oxidative stress along with the production of free radicals [77].

4.4.1. Lead

Low- level lead exposures can interfere with cognitive function in children. Extensive evidence also shows that past adult lead exposure in the work setting increases the likelihood of cognitive impairment [87]. Lead intervenes with visual-spatial and visual-motor functions. Individuals who are exposed to lead show slower language processing speed.

A variety of mechanisms may contribute to lead neurotoxicity. Lead can cross the blood brain barrier in various forms. It has the potential to destroy calcium-dependent enzymes, neurotransmitter metabolism, synaptic transmission and plasticity, oxidative phosphorylation, glucose oxidation, and microtubule synthesis. It can also cause neural oxidative stress [88]. This leads to the aggregation of beta-amyloid protein [89]. Studies have shown that one's lifestyle in one's early age predisposes to adult disease. Fetal rodents when exposed to lead developed proteins responsible for Alzheimer's disease in their neonatal life. Interestingly, exposure to lead during old age did not cause increases in the Alzheimer's disease–related proteins. These are popularly known as "amyloid precursor proteins", which lead to the production of amyloid-beta [81].

4.4.2. Pesticides

Since many pesticides work through on neurotoxic pathways, occupational exposure to pesticides increases the risk for Alzheimer's disease. Studies show that moderate as well as high-level pesticide exposure is neurotoxic [80].

4.5. Gender

There seems to be a general consensus that AD affects more women than men. Though the principal reason as to why this is so has not been fully explicated, a research study conducted by the Framingham Heart Study hypothesized that men over the ages of 65 have lower chance of suffering from cardiovascular disease than women within the same age range, thereby leading to men having lower dementia risk than women. Then there is also the issue of educational attainment. It is postulated that men in the early part of the 20th century attained a higher educational accomplishment than women. This will probably mean that their cognitive usage was more than women, thus having less chance of getting AD. It is nevertheless yet to be scientifically proven [86]. Research papers have also attributed that the APOE-4 variant does interact with the primary female sex hormone, estrogen, and as such could also possibly be the reason as to why more women suffer from AD than men [86].

5. The AD Pathology

What then really happens in the brain of an AD patient? As stated earlier, tangles and plaques are formed in an Alzheimer's patient's brain. These tangles and plaques disrupt the communication of the cells by interfering the normal function of the brain cells. Consider sitting in an airplane and looking down to a large city with various homes, business places, streetlights, libraries, cinema and schools having its own light bulb and switch. These lights play an important role in the normal daily activities of the people in the city. Moreover, from the airplane, one can see

that the city flow as a result of the lights coming from all these places: the homes, school and business places. Then all of a sudden, a fault appears in the circuits of the city's electrical power. There is no power to cook food; street lights are not working and such no driving can take place. School and business places are being sabotaged by this power break. In the nutshell, there is inference in the normal daily activities of the people in the city. Sooner or later, the power outage incapacitates the once beautiful and vibrant city along with its people [25]. This is the same scenario that takes place in AD brain. The human brain has about 100 billion nerve cells that communicate with each other through chemicals known as neurotransmitters, performing different functions such as remembering names of people and places, planning future events, controlling emotions and making judgements, be it good or bad, thereby helping in the daily lives of humans. The neurons represent the lights in the 'city' analogy. With time, the neurons in the Alzheimer's brain are turned off, thereby interfering with the cell communication and further resulting in thinking, communication and remembering problems. More so, the Alzheimer's brain tissue is generally shrunk, with the most severe shrinkage occurring in the hippocampus. The hippocampus, located in the cerebral cortex, aside being involved in temperature regulation is also responsible for the formation of memories [25, 27, 61, 64].
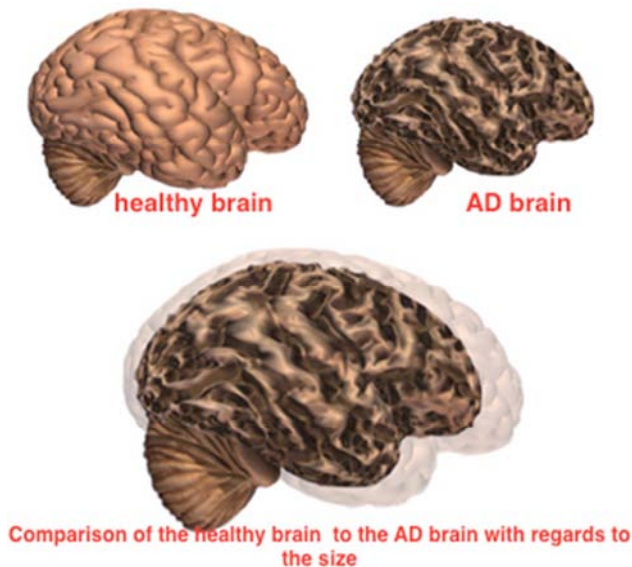

Figure 6. *The difference between a healthy brain and an AD brain [18].*

Despite the issue with the death of neurons along with the shrinkage of brain tissues not well understood yet, the neurofibrillary tangles and the amyloid plaques continue to be the chief suspects with the following being suggested: the amyloid plaques inhibits the signal activities of the cell, possibly eliciting inflammation which in turn annihilate the inhibited cells. The neurofibrillary tangles on the other hand, has been found to be involved in the destruction of the cell transport system, which is comprised of proteins. The healthy human brain can be related to a good railroad track as shown

in figure 7 below. Essential materials like food molecules and cell parts use this railroad track to get to their destination, the cells, with the tau protein serving as the maintenance man, keeping the track straight. However, the formation of neurofibrillary tangles leads to the demise of the maintenance man, tau protein, this results in the breakdown of the track which in turn ultimately leads to the death of the cells as the essential materials needed are no longer able to use the railroad track to get to their destination [62–63].
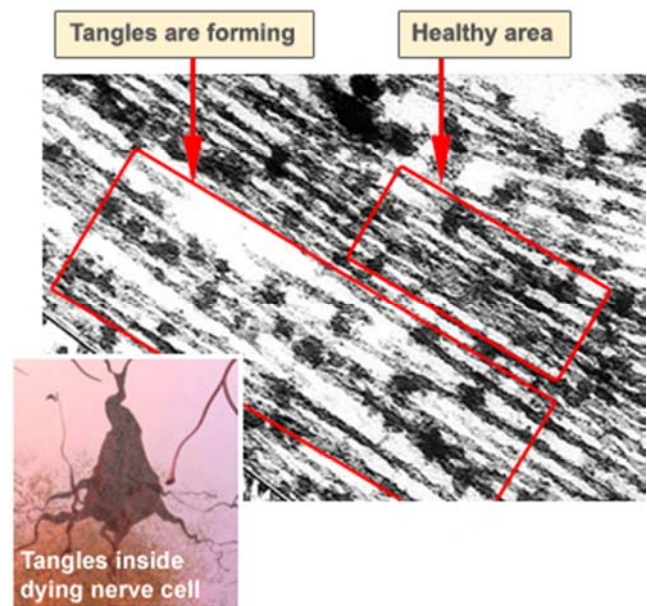

Figure 7. *The neurofibrillary tangle formation [62].*

6. The Cholinergic Hypothesis

Deficiencies in cholinergic and excitatory amino acid neurotransmission have been associated with a weaker in memory and decline in learning [100]. Biochemical and pathological studies suggest that the deterioration of cholinergic neurons in the basal forebrain, and hence the loss of cholinergic neurotransmission in the cerebral cortex contributed significantly to the decline of cognitive function seen in the patients suffering from Alzheimer's disease [101].

The period between the early 1960's to mid 80's was the "golden age" for study of neurotransmitters. Researches during this period had successfully discovered and characterized important neurotransmitters and their receptors. They further encoded the neurotransmitter systems underlying specific nervous connections and brain functions [102]. The intrinsic therapeutic idea behind the studies related to neurotransmitters was that this knowledge could guide scientists to develop rational therapeutic disease approaches targeted at the correction of the neurochemical alterations in a patient's brain. This method did enable the cholinergic hypothesis to gain momentum. The pathological samples from the cortex and hippocampus of the brains of Alzheimer's patients showed a significant decrease in choline acetyltransferase. Choline acetyl transferase is the enzyme responsible for the synthesis of acetylcholine [103].

In the late 80's, it was reported that cortical choline acetyltransferase activity experienced a reduction (similar to the case in Alzheimer's disease patients) in the brain of patients with inherited Olivopontocerebellar atrophy (hereafter: OPA). Although there was a drop in the level of choline acetyltransferase, the patients with inherited OPA did not suffer from dementia [104].

Scientists suggested that hippocampal enzyme activity was unchanged in patients with OPA, in the bargain, suggesting a remarkable involvement of the damage to the cholinergic septo-hippocampal projection in Alzheimer's disease. In the recent years due to the availability of diagnosis of early stage of Alzheimer's disease, researchers have suggested that there is no significant decrease in the activity of choline acetyltransferase [105–106].

Another perspective suggests that the impairment of short term memory characterizing may be with regards to the reduction of the entorhinal-hippocampal connection instead of the alteration of the septo-hippocampal cholinergic system [107].

Cholinergic hypothesis has travelled a long way and has also paved a new path for scientists to tread on to explore and hopefully find the cure of Alzheimer's disease in the future.

7. The Current Treatment Methods

In spite of being no cure presently for AD, the approved medications by the FDA as stated earlier on helps in delaying the degenerative symptoms associated with the disease.

Donepezil, Rivastigmine and Galantamine are all cholinesterase inhibitors used in the treatment of mild to moderately severe Alzheimer's [26]. As mentioned earlier on, communications within the brain tissue are made possible with the help of neurotransmitters. Take a person who recently underwent surgery to amputate their legs. Upon recovery, they have to find a way walking and moving from one place to the other as such require the help of crutches. Similarly in the brain tissues, the communication from one cell to the next is by means of an electrical medium. However the force needed for communication from one cell to the other is not enough and as such requires extra help. This is when neurotransmitters come in. The brain employs various neurotransmitters in performing different functions and evidently their ineptness is detrimental. The first neurotransmitter to be tied to AD, acetylcholine, has been stated in research papers as being severely impeded as compared to the other neurotransmitters found in the brain. Acetylcholine most importantly is involved in the memory and thinking department of the brain [27, 52]. Now, after helping in the transmission of messages between neurons, the acetylcholine is annihilated by the enzyme, cholinesterase. This is to prevent problems such as seizures occurring since if acetylcholine is not annulled, it will continue to send the same message over and over again. With AD however, as the disease continue to gain momentum, the work of the acetylcholine is hindered bit by bit. This leads to the introduction of cholinesterase inhibitors. The cholinesterase inhibitors aim is to avert the destruction of the limited acetylcholine remaining so as to allow the continuation of communication between cells. Interestingly, the receptors that work with acetylcholine also welcome molecules of nicotine. Hence, the reason why smoking is noted as one of the probable causative factor in the development of the disease [27].

The three medications, Donepezil, Rivastigmine and Galantamine, have the same mode of action, however both their pharmacodynamics and pharmacokinetics characteristics vary. Suggested side effects of cholinesterase inhibitors include nausea, dizziness, anorexia and insomnia with respect to the drug, patient and the regimen [26, 65].

Table 3. Summarization of Pharmacokinetics and Pharmacodynamics properties of the Cholinesterase Inhibitors [26, 65].

	Donepezil	Rivastigmine	Galantamine
Enzymes impeded	Acetylcholinesterase	Acetylcholinesterase and Butyrylcholinesterase	Acetylcholinesterase
Enzyme Impediment mechanism	Uncompetitive Reversible	Uncompetitive Irreversible	Competitive Reversible
Half-life (mins)	Between 3000 and 4800	Between 4 and 120	Between 420 and 480
Bioavailability	100%	In the range of 35 to 40%	100%
Plasma Protein Binding	About 96%	About 40%	About 18%
Dosage (mg/day)	Between 5 and 10	Between 6 and 12	Between 16 and 24

Glutamate, the other neurotransmitter connected to AD, aside helping in the communication between neurons is also involved in several metabolic functions [27, 28]. However, when its work is done, instead of being terminated like acetylcholine, it is rather reprocessed by coupling with the N-Methyl-D-Aspartate receptors. Nonetheless, when a dysfunction in the neuron arises, glutamate oozes out of the neurons, with studies showing that excess of this can cause the death of the neurons, a process known as excitotoxicity.

This is when Memantine, the other FDA approved drug for moderate AD steps in. Its work is to obstruct the production of excess glutamate while granting the admittance of adequate glutamate into the neurons for communication purposes as well as the other functions associated with it [27].

8. The Preventive Mechanisms of AD

In the same way there are treatment comes, there are also some suggested preventive mechanisms that reduce the likelihood of developing AD. Again, as the disease has not been well understood, it is unclear at the moment which of the preventive mechanisms is more effective or better than the other. Nevertheless, some of the preventive mechanisms suggested are centered on lifestyle changes and diet [22].

The lifestyle changes include mental and physical

exercises. Mental exercises such as general reading, playing board games as well as playing instruments helps in keeping the brain active, thereby reducing the risk of getting AD. Besides enhancing the blood flow, physical exercise also aids in the oxygen flow within the brain tissues, which in turn decreases the risk of developing the disease [22].

In the dietary department, the Mediterranean diet, of which constitutes a small amount of red meat coupled with conglomerations of fruits, vegetables, whole grains, fish and shellfish as well as healthy fats, has been suggested to have a hand in delaying the cognitive atrophy symptom associated with AD [29]. Other research studies have also postulated that by lowering the homocysteine levels, an amino acid that is obtained predominantly from the consumption of meat, in the blood, the risk of getting AD will reduce [30].

9. The Future of AD

Current independent and drug manufacturing company researchers are focusing on the two prime suspects linked to the AD, which are the neurofibrillary tangles and the amyloid plaques. There is the notion that a treatment method that inhibits the formation of both the neurofibrillary tangles and the amyloid plaques will go a long way in possibly halting the progression of AD. Drugs currently being researched include MK-8931, CSP-1103, Pioglitazone, Saracatinib, Aducanumab, Solanezumab, AADvac1 and intranasal insulin [34–35]. These drugs are generally classified as disease-modifying drugs. Regarding disease-modifying drugs, its main aim does not lie in curing the disease completely but rather slow down the deterioration. In other words, these drugs help delay the inevitability. As these drugs slow down the disease, its benefit is only temporal. Researches are however optimistic that in the near future disease modifying drugs will be able to completely thwart the concatenation of AD.

Beta secretase is one of the enzymes responsible for interfering with the APP gene, resulting in the formation of the amyloid plaques. As such a beta secretase inhibitor aim will be to impede this process, thereby reducing the anomalistic production of the beta amyloid in the brain, which in the long run will interrupt the progression of AD [34]. The current researched beta secretase inhibitor is the MK-8931 with preliminary results released at the Alzheimer's Association International Conference (hereafter: AAIC) in 2013 showing reduced levels of the beta amyloid plaques in mild to moderate AD patients. MK-8931 is currently undergoing Phase 3 clinical trial [34].

Another key component in an Alzheimer's brain is inflammation [52]. The formation of beta amyloid plaques and neurofibrillary tangles results in an immune response in the brain. Microglia, the cells that serve as the principal immune defense in the brain assists in the removal of the beta amyloid in the brain. However, abnormal production of the beta amyloid in the brain can lead to the microglia being hyper, thereby leading to the production of chemicals that destroy neighbouring cells [34, 53, 54, 56]. The CSP-1103 is a current researched drug that looks to combat this neuro-inflammation. Initial clinical trial results put forward at the AAIC in both 2013 and 2014 demonstrated vital improvement in the cognitive skills of the clinical trial participants. CSP-1103, at the present, is undergoing Phase 3 clinical trial [34, 37]. Additionally, another drug being researched and which also aims to solve the inflammatory process related to AD is the diabetic drug, Pioglitazone, which presently bears the brand name "Actos" [35–36].

There is also the issue with Fyn, a tyrosine kinase, which has been suggested to have a role in the phosphorylation of the tau protein, further leading to AD [38]. Other research papers have hypothesized that Fyn becomes hyperactive when mingled with beta-amyloid. The hyper-activation of Fyn sparks the extirpation of networks between the brain neurons [35]. Interestingly, Saracatinib, a drug that was initially being developed for the treatment of cancer, when tested on mice halted the tyrosine kinase, Fyn, leading to the reactivation of the brain neurons along with the mice regaining some of the memory loss [39, 55]. Presently, a human clinical trial is ongoing to test the drug in AD [35, 40].

Solanezumab, a monoclonal antibody, is being developed with the aim of reducing the beta amyloid that is formed AD brain. Initially, it was being designed for the treatment of mild to moderate AD, however, during its Phase 3 clinical trial, the drug displayed an unsatisfactory efficacy result. As such, it is now being investigated for the treatment of mild AD [41–42]. Solanezumab generally attaches itself to the beta amyloid, inhibiting the formation of the amyloid plaques. The current research of Solanezumab drug centres on improving both the cognitive and functioning abilities of clinical trial participants [42].

The other monoclonal antibody drug also currently under investigation with the aim of tackling the amyloid plaque is Aducanumab. Encouraging preliminary clinical trial results of the drug was presented at the 12th International Conference on Alzheimer's and Parkinson's disease and Related Neurological Disorders held in France on 25th March 2015. The beauty of the presented clinical studies of the Aducanumab was the effectiveness of the drug on participants irrespective of their APOE status, be it carrier or non-carrier, as well as the progression of the disease [43–44].

The tau vaccine, known as AADvac1, is a vaccine currently being experimented for the treatment of AD. It works by triggering the immune system to vilify the defective tau protein that destroys the nerve cells in the brain, thereby stopping the progression of AD. The present research is focused on assessing the effect of the AADvac1 vaccine in hindering the cognitive deterioration in AD patients [34].

Ladostigil is another disease modifying drug that is currently undergoing clinical trial for the treatment of MCI by Avraham Pharmaceuticals. It is presently in the Phase 2b stage of the trial and is being assessed for its effectiveness as well as safety. Structurally, it is composed of two portions, a Carbamate portion and a Propargyline portion. The Carbamate portion is a cholinesterase (i.e. acetyl

cholinesterase and butyl cholinesterase inhibitors) with the Propargyline portion being a selective monoamine oxidase B inhibitor. As a result of it comprising two portions, Ladostigil is viewed as a multi-functional drug. Originally, the motif of the drug was to act as both cholinesterase as well as a selective monoamine oxidase inhibitor in the treatment of AD in high dose. However, the results obtained from the Phase 2b clinical trial study in 2012 was not in accordance with its primary goal, hence the administered dose was lowered a new study commenced. The second interim result from the Phase 2b trials following the reduction in drug dose has been encouraging, especially for the fact being that no complications from the usage of the drug has been reported so far. With the reduction of drug dose, Ladostigil has been found to not only truncate the oxidative stress as well as microglia activation associated with AD but also bridle the inflammation caused in AD brains. Brain inflammation is one of the trademarks of AD and is thought to be stimulated by cytokines such as IL-18, IL-10, IL-6, TNF-α and IL-1β. Interestingly the drug following its reductions in dose did not suppress the enzymes cholinesterase and selective monoamine oxidase. The successfulness of Ladostigil in the clinical trials will lead to its usage in impeding on the degeneration in MCI as well as preventing the progression of MCI into AD [98, 99, 108].
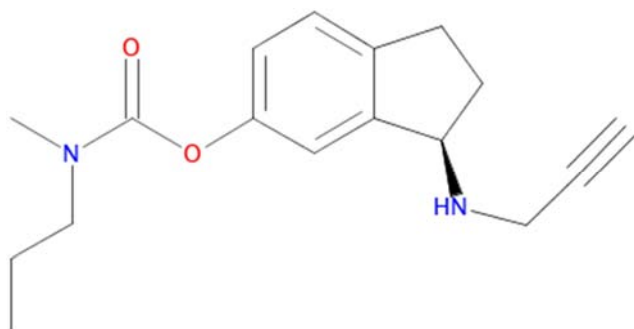

Figure 8. Structure of Ladostigil.

Passive Immunization is also one of the current treatment options for AD being looked into. It involves the use of injections of beta amyloid antibodies. Initially, active immunization, which involved the use of beta amyloid, was employed and although it reduced the agglomerated amyloid plaques by forming antibodies against the amyloid beta precursor protein, there was the issue of severe brain inflammation found in roughly 6% of the people who took part in the clinical trial. Thus, the cessation of the active immunization method and the birth of passive immunization [45].

9.1. Epigenetics

Epigenetics has to do with the alteration in the gene function without any modifications in the principal DNA sequence. Genetic modifications can lead to contrasting behavior of organism genes. Histone modification, DNA methylation and miRNA's are the three distinct areas of epigenetics heavily being involved in research studies with the most investigated one being DNA methylation. Though yet to be fully elucidated, research studies conducted within the last decade links epigenetics as having a role in the pathogenesis of AD along with other neurodegenerative diseases such as Parkinson's and Huntington's diseases.

DNA methylation has been implicated to have an involvement in memory function. Research papers have attributed the atrophy of memory together with learning adroitness to the deterioration of age, which in turn truncate DNA methylation. Histone acetylation, which is also thought to be incriminated in the modulation of learning and memory functions of the brain is catalyzed by the enzymes histone acetyltransferase (HAT) and histone deacetylases (HDAC's). Presently, the number of human related HDAC's is 18, categorized into 4 classes, with class 2 further grouped into 2 [110–111].
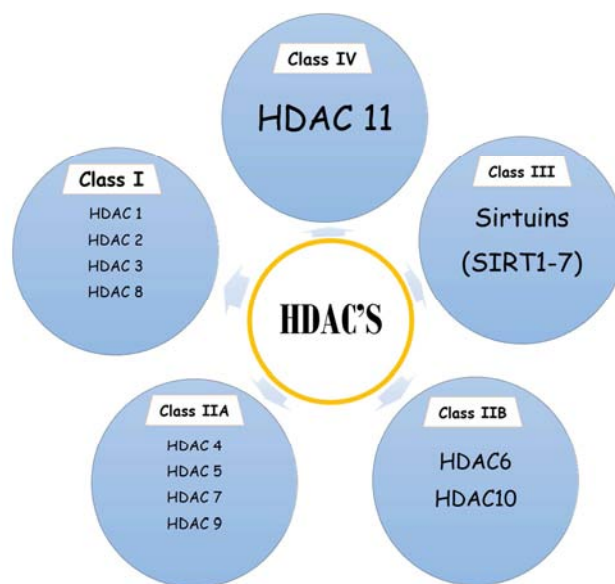

Figure 9. Classification of HDAC's [111].

HDAC 2, which belongs to class 1 HDAC's, has been postulated to be involved in memory impairment in mice. Current epigenetic therapeutics being investigated includes trichostatin A, nicotinamide, betaine and curcumin [111].

Trichostatin A (hereafter: TSA), an HDAC inhibitor has been suggested to play a role in hindering beta amyloid plaques and tau hyperphosphorylation. The protein, gelsolin, which is thought to be abridged in the brains of AD patients, has been reported to help in relieving the amyloid plaques found in AD brains. In a 2014 published study, TSA was found to escalate the gelsolin levels in models models by almost two folds. As such TSA has the potentiality of being employed in the treatment of AD [112].

Betaine, a DNMT, is a therapeutic agent that researchers are looking into for the treatment of AD. Homocysteine levels have been found to be elevated in AD patients, which in turn possibly results in the formation of beta amyloid plaques and tau phosphorylation. In a recent study, betaine was reported to curtail the homocysteine levels and

subsequently improved the memory decline in rats [113].

Curcumin, an HAT inhibitor belonging to the plant family Zingiberaceae, has also been hypothesized to have the potentiality of serving as neuroprotection against AD. In Indian particularly, curcumin segregated from the root of the turmeric plant, is found in food substances such as curries. A couple of research studies conducted have reported curcumin to counter the oxidative stress associated with AD besides impeding on the amyloid beta plaques, one of the hallmarks of AD. Moreover, curcumin has been discovered to inhibit the cytokinesis, IL-1β, IL-6 and TNF that are implicated to cause inflammation in AD brains. Despite all these reports, more clinical studies are indispensable to ascertain the effectiveness in the clinical settings [114].

Nicotinaminde, an SIRT inhibitor and a vitamin B component, specifically vitamin B_3, has been reported to have an AD therapeutic prospect. The copious research studies on nicotinamide have discovered the tau phosphorylation connected to AD to be impeded by nicotinamide. The tau protein is associated with microtubule formation. As such when nicotinamide hinders the tau phosphorylation, more specifically the Thr231 phospho-tau that dismantles these microtubules, the neuronal communication disintegration as a result of tau phosphorylation is averted. Other published studies have also reported synaptic plasticity re-imposition through the use of nicotinamide. Interestingly, there was no interference on the beta amyloid plaques by the nicotinamide [17, 115–117].

9.2. Gene Therapy

Gene therapy is also one of the rapid research areas researchers and scientists are looking into in finding a cure for AD. Genes are located in the nucleus of a cell and are responsible for carrying the genetic make-up of an individual or species. Gene therapy generally is the alteration of an individual's genes to either treat or prevent diseases. The alteration is done by removing faulty or diseased genes and inserting a healthy gene using viral vectors. In short, viral vectors are gene delivery trucks. The initial idea behind gene therapy was to be able to employ it in the treatment of inherited diseases such as cystic fibrosis, however the horizon has broadened to include other diseases such as cancer as well as neurodegenerative diseases like AD [118].

In 2005, researchers conducted the first study on eight AD patients using gene therapy. Though the disease was not cured, the mental deterioration associated with the disease was hampered coupled with amelioration of metabolic activities within the brain [119]. Following that, several scientific studies have been conducted on mice with propitious results. Some of the results gathered include the backtracking of the loss of synapses and memory, alleviation of amyloid beta sediments as well as the extrication of degenerated cells in AD brains [50–51]. As recent as October 2016, researchers halted the progression of AD using gene therapy. The PGC-1-alpha gene was used in the hippocampal and cortex regions of the brain with the aid of a lentivirus vector. Results from the study evinced the obstruction of the

formation of amyloid beta proteins together with a diminution of glial cells. Amyloid beta proteins are the chief constituents of amyloid plaques discovered in AD brains and leads to tau phosphorylation. In addition to no reported degeneracy of brain cells in the hippocampal region of treated mice, they also executed better memory functions in contrast to the untreated mice, which could be attributed to the emergence of low amyloid beta proteins in the treated mice. Glial cells on the other hand have been postulated to extricate noxious inflammatory cells that cause damage to neurons [120–121].

10. Conclusion

Despite the fact that AD is still not wholly understood as of now, the future does look promising in finding its cure in a sense that compared to more than 100 years ago when the first case of AD was documented, there has been an outstanding progress in first and foremost understanding the function of the brain and subsequently gaining a much better understanding of the AD as well as the Alzheimer's brain. More so, there are substantial knowledge relating to ways, to a certain degree, that can reduce the chances of getting AD.

In conclusion, considering all the current research studies underway, along with the attention AD is attracting, there is a high possibility in about 10 to 15 years from now, the myths surrounding the AD regarding its full understanding, causes and preventive mechanisms would have been unraveled together with effective treatment measures to completely eliminating the progression of the disease put in place.

Acknowledgements and Dedication

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