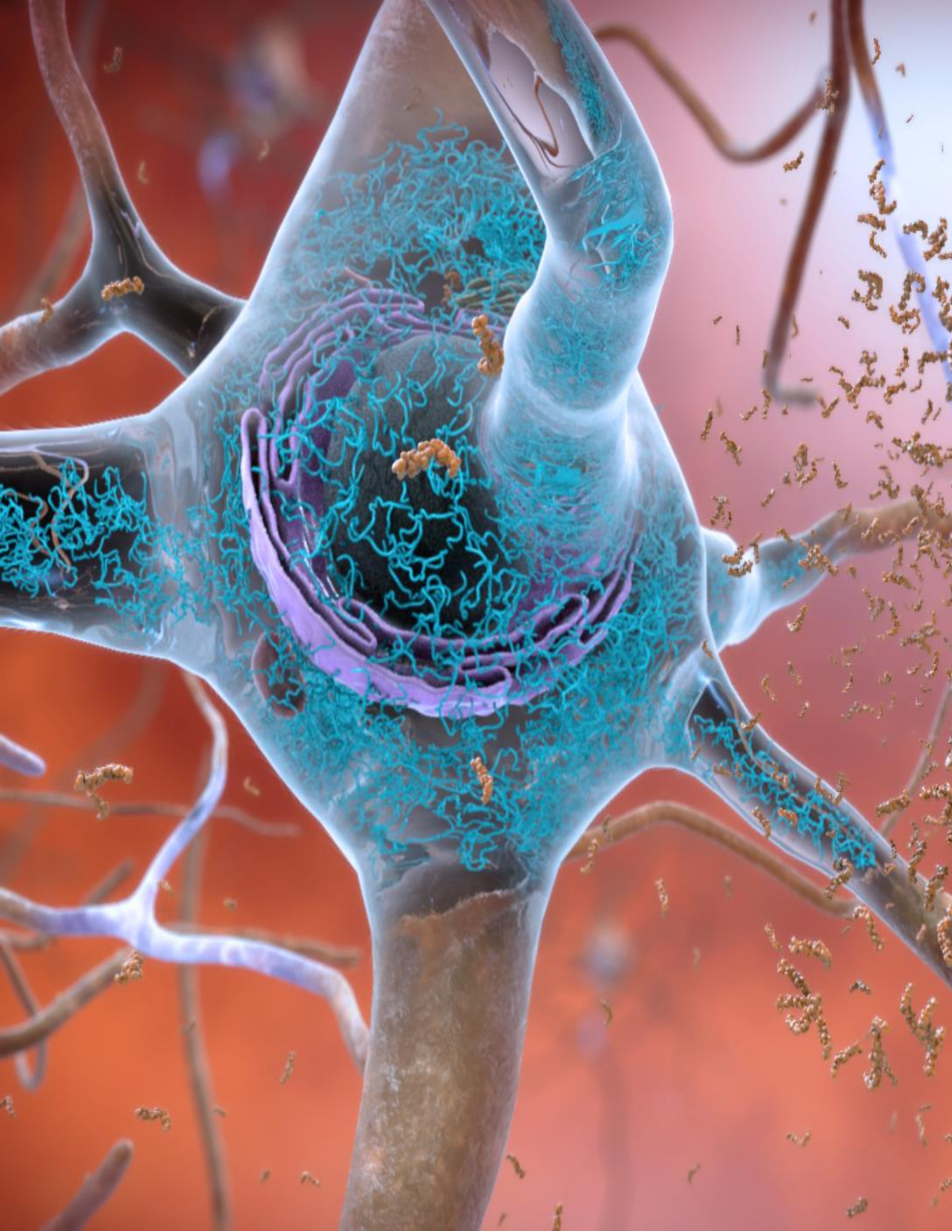

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Current Advances in Alzheimer's Disease

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ISSN-2767-5041

Table of Contents

ISSN-2767-5041

ISSN-2767-5041

Abstract

While there have been enormous advances in therapeutics and translational medicine, with reduced rates of morbidity and mortality in many cases, there has been an unfortunate increase in the number of age related disorders. In particular, Alzheimer's disease (AD) is a progressive disorder of the brain, exhibiting a neurodegenerative cascade leading to terminal dementia in most cases. This paper evaluates the pathophysiology, risk factors, diagnosis, prevention, and epidemiology of this disease.

Alzheimer's Disease

The terminology was derived from the neuroanatomist and clinical psychiatrist Alois Alzheimer. They reported "A peculiar severe disease process of the cerebral cortex" in a 50 year old woman at the 37th meeting of Psychiatrist in Tubingen, Germany, in 1906. Since then, the autopsy samples are used to detect the clinical outcome of the disease. The public health impact of AD is huge, considering it to be the most common cause (60-80%) of dementia-related diseases in the world with no known cure. This disease places a high social burden on both patients and care-givers. Recent improvements in medical diagnostics allow *in vitro* testing of cerebrospinal fluid and serum in both susceptible individuals and symptomatic patients with a background history of primary risk factors.

There are two distinct classifications of AD: early or familial AD and late-onset AD or sporadic AD. The late-onset AD covers around 90% of the cases. The number of expected diseased individuals in the age group 65 years and above will grow to almost fourteen million among Americans by the year 2050. This is an abrupt increase from the current scenario, eclipsing other causes of death like HIV, stroke, and heart diseases. A recent estimate is that someone will

ISSN-2767-5041

develop the disease in 66 seconds; however, by 2050, every new case of AD will occur in only 33 seconds [1].

Early onset AD, also known as familial AD, is a genetic disease showing trends of gradual cognitive impairment and sensory dysfunctions for people under the age of 65. A rare dominant mutation in the autosomal fragments of three chromosomes occurs, and it is suggested that these mutations play a role in familial AD. Either of the two presenilin genes (PSEN1 and PSEN2) on chromosomes 1 or 14 or the amyloid precursor protein (APP) gene on chromosome 21 acts as a genetic predisposition for AD. On the other hand, the genetic causes of late onset AD or sporadic AD are not well understood, but APOEε3 and APOEε4 has been defined as a risk gene for many cases of late onset AD. Early symptoms define the reduced ability to encode and store new memories [2]. The cognitive dysfunction stage predominates with signs of anxiety, agitation, apathy, irritability along with depression. Often hallucination and olfactory disturbances are also observed. AD is the most common form of irreversible dementia, which is found in around 70% of all dementia cases in the US.

Pathophysiology of AD

Degeneration initiates in the entorhinal cortex and hippocampus of the temporal lobe of brain, which is an important area of functioning in memory and learning functions. Subsequently, degeneration spreads to associated cortex and to parietal areas. Furthermore, pathophysiological lesions are observed in the frontal cortex and in most of the remaining neocortex. Subsequent damage to hippocampal formation and the major fiber tracts are also observed as the disease spreads. The scenario worsens when neurodegeneration extends to the amygdala, cingulate gyrus, and thalamus. The widespread nature of neurodegeneration affects both areas of the

ISSN-2767-5041

limbic and neocortical regions of the brain. These areas have significant cognitive deficits and behavioral functions (Figure 1) [3].

Figure 1. Stages of neurodegeneration in AD [Ref 4]

In classical AD, the manifestations of atrophy and chronic inflammation in various regions of brain are observed due to the inability of the microglial cells to remove toxic proteins and dead cells. Microglia in the brain removes cell debris, infection and damaged neurons for maintaining healthy functioning of the central nervous system. They are specialized macrophage cells. Depleting microglia in animal models of AD prevented the accumulation of amyloid plaques in the parenchymal space. The majority of risk genes for AD are highly expressed by microglia in the brain. There is evidence that microglia protect against the incidence of AD. Conversely, there is also evidence that activated microglia can be harmful to neurons [5]. In AD, the role of secretion of cytokines and higher release of free oxygen species leads to oxidative damage and consequent astrocyte damage, which are the supporting cells to neurons in signal transmission cascade. Thus, a multifaceted mechanism emerges both at the histological and cellular levels to define AD pathophysiology.

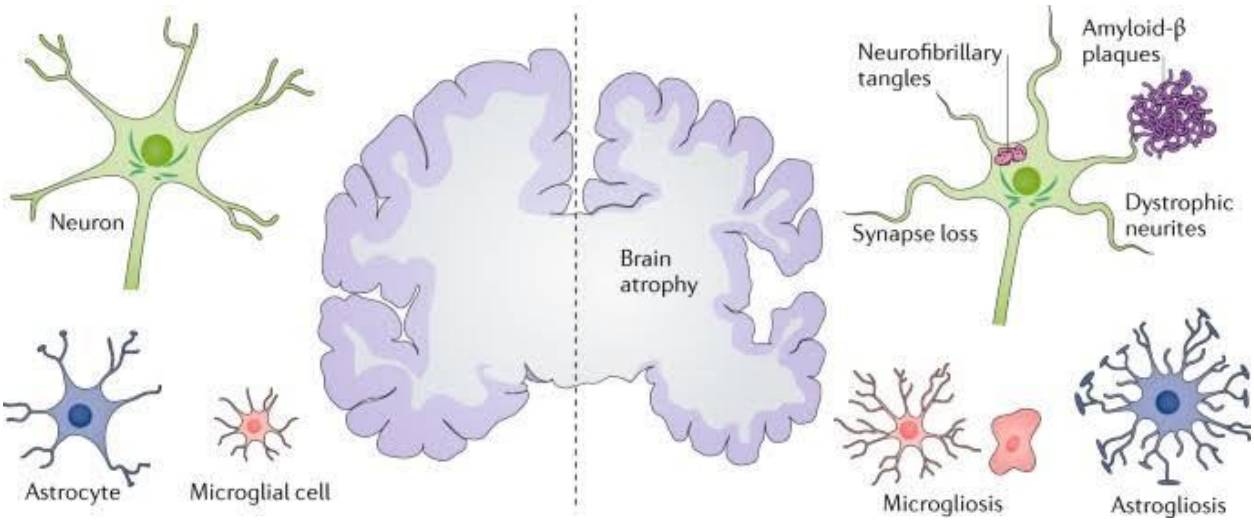

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Figure 2. The pathophysiology of Brain in normal versus patients with AD [Ref 6]

More specifically, when considering the characteristics of AD pathophysiology, the hyperaccumulation of fragment beta-amyloid (Aβ) and hyperphosphorylated tau protein aggregation should be considered. Early diagnosis is difficult considering the slow progression of this disease. Several potential markers indicative of alterations in redox potentials along with protein dysfunctions are present in the neuronal mitochondria [7]. The prominence of Aβ deposition, pathologic tau in the brain, and neurodegeneration [AT(N)] through neuroimaging and biofluidics have been critical biomarkers as suggested by the National Institute on Aging and Alzheimer's Association Research Framework. The focus of the diagnosis has changed from a clinical symptomatic construct to defining biological construct in living person (Figure 2) [8].

Aβ or amyloid beta plaques

Amyloid beta plaques are extracellular protein complexes of amyloid protein, whose main constituent is the beta amyloid structure proteins formed from the cleavage of the amyloid precursor protein (APP). Under normal functioning, APP is cleaved by enzymes on the membrane surface to secrete soluble amyloid beta proteins, but in a diseased state, the mutation results in abnormal cleavage of APP, resulting in dense insoluble beta sheets and subsequent plaque formations [3]. It is also thought that the disruption of axonal transport results in the autophagocytosis of mitochondria without normal lysosomal degradation within the cells, which may result in the formation of amyloid (Figure 3) [9, 10].

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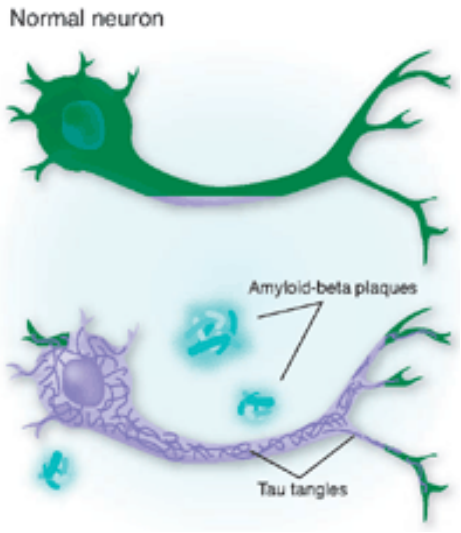

Figure 3. Intracellular neurofibrillary tangles and extracellular amyloid β plaques[Ref 10]

'Neurofibrillary tangles' (NFT) are aggregates of abnormally hyper-phosphorylated protein tau, which is formed intracellularly. In normal physiological condition, tau protein serves as a microtubule stabilizing protein in the axonal part. The tau protein has a vital role in axonal and vesicular transport [10]. It is considered that NFT interferes with normal axonal transport, resulting in neuronal death. The pathological features show the presence of high amounts of NFT in the amygdala, basal nucleus of Meynert, the locus coeruleus, substantia nigra along with dorsal raphe nucleus and hypothalamus of patients with AD. In particular, neurites in the basal nucleus of Meynert and locus coeruleus have been demonstrated to be associated with progression of AD dementia [11]. Recent research suggests that restoration of mitochondrial function by physical exercise, an antioxidant diet, or therapeutic approaches can delay the onset and slow down the progression of AD [12].

ISSN-2767-5041

Risk factors associated to AD

There are chronic underlying risk factors including smoking, diabetes, hypertension, obesity, and hypercholesterolemia with respect to the development of AD. In addition, patients having a history of depression, head injury along with ischemic strokes and sleep apnea syndrome have statistically been associated with the development of AD (Table 1) .

The onset of AD is also thought to be higher in the female population compared to male population. The theory is that women typically live longer than men. It is believed that education and engagement in cognitive activities creates reserves and resilience to impede the development of AD dementia in later life [3]. Some lesser risk factors include loss of hearing, occupational exposures to magnetic fields, hyperhomocysteinemia, and some forms of essential tremors. Exposure to pesticides is also associated with increased risk of AD. Moreover, excessive alcohol consumption is associated with AD development and progression [13].

Smoking

Smoking is a repetitive habit of consuming tobacco leading to chronic exposures to different types of combustion products. There is a risk of developing AD in people with a previous history of smoking. Smoking habits have been associated with increased blood pressure, pulmonary

ISSN-2767-5041

disorders and heart problems which are indicative of increased levels of oxidative stress. Those stresses correlate to potentially developing AD. Based on forty three international cohort as well as case-controlled studies for a 25 year period, Cataldo *et al*, 2010 demonstrated that smoking is a risk factor in developing AD [14]. Smoking is one of the modifiable risk factors. Lifetime smokers are associated with approximately 70% greater risk for contracting AD than non-smokers.

Table 1: Major Risk Factors association to AD

Major Risk Factors	Underlying causes to AD development	Modifiable (Yes/No)	References
Smoking	Increasing atrophy and reduced cortical region grey matter	Yes	Ref 14
Lack of physical exercise	Decreases hippocampal volume and cerebral blood flow and cognitive impairment	Yes	Ref 15
Diabetes	Leads to insulin resistance and glucotoxicity in hippocampus leading to memory impairment	No	Ref 17
Obesity	Neuroinflammation due to excessive adipokine secretion crossing blood brain barrier leading to cognitive dysfunction	Yes	Ref 19
Hypertension	Hypertension has interactive contribution with vascular dementia	Yes	Ref 20
Head Injury	Traumatic hemorrhage or vascular leakage leads to inflammation and neuronal damage along with over-expression of the β-APP	Yes	Ref 22
Sleep Apnea	Hypoxia related pathophysiology leading reduced clearance to production-clearance dynamics of Aβ due to fragmented sleep	Yes	Ref 23
Depression	Emotional disturbances leads to cognitive impairment	Yes	Ref 24

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Lack of physical activities

There is an increased risk of AD onset in people who do not have a routine physical exercise regimen. Exercise increases cognitive functional abilities. It increases cerebral blood flow which leads to neurogenesis [15]. Current literature indicates that physical exercise and fitness is associated with improved cognitive function. The cerebral flow of blood is higher in the anterior cingulate cortex of the brain during work out, which is primarily related to increase in happiness and emotional stability. Lack of activity is associated with emotional suppression. Chapman *et al.* demonstrated that a twelve week regime of exercise in a randomized trial brought enhanced blood flow in the anterior cingulate cortex of individuals following the regimen compared with the control groups. Moreover, the hippocampal circuits responsible for episodic-like memory are affected initially in AD. These cognitive effects can be mitigated through moderate exercise. It was also found that the risk of AD can be lowered 45% with physical activity.

Diabetes

Hyperglycemia is an imbalance in glucose homeostasis in patients with diabetes. The glucotoxicity affects peripheral tissues and vessels, leading to pathological complications including diabetic neuropathy. The toxic levels of glucose initially affect the pancreas and liver, and progressively affects other organs like the brain, heart and kidneys. Glucotoxicity results in structural damage to brain cells through mitochondrial stress and dysfunction, functional impairment of neurons, inability to transport insulin in acute hyperinsulinemia for glucose level control, cerebral hemorrhage and enhanced accumulation of amyloid beta proteins due to inhibition of APP degradation [16]. Patients with severe hyperglycemia demonstrate deteriorating cognitive functions and various other facets of mental health due to significant damage in the hippocampal region, the area of the brain responsible for memory function. A

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study by Irie *et al*., described the underlying risk factor as diabetes mellitus type II being associated with incidences of AD-related dementia during an observational period of seven years [17].

Obesity

Obesity is a risk factor associated with AD. Further prevention to late onset of AD can be achieved through midlife management of obesity. Weight management through exercise and proper diet is paramount to healthy living. Adipocyte dysfunction and adipocytokines or adipokines are the major players thought to contribute to neuropathy in obese patients. Resistin (adipose tissue-specific secretory factor) and leptin like adipocytokines are secreted in elevated levels in dysfunctional adipose tissue along with reduced secretion of adiponectin and anti-inflammatory molecules. This leads to neuroinflammation which may influence cognitive-related structures of the brain [18]. A proportional hazards model demonstrated that one unit less body mass index or BMI was associated with about a 5% increase in the risk of AD [19].

Hypertension and Hypercholesterolemia

Hypertension, or high blood pressure, is a key factor in the development of cardiac disorders. Case studies have demonstrated that midlife stage systolic hypertension is associated with an increased risk of AD of up to 25% [20]. There is no strong evidence of an association between hypercholesterolemia and development of AD as increased serum and cerebrospinal fluid levels of cholesterol have minimal effects on late onset of AD.

Head Injury

Many case-control studies have shown that a history of head injury is prevalent among patients with AD in comparison with healthy elderly individuals as controls. In addition, the most common non-genetic factor is head injury. Further recent meta-analysis of the literature,

ISSN-2767-5041

investigated over a period of 25 years, revealed that head injury significantly enhances the risk of AD [21, 22].

Sleep Apnea

Sleep disorders in the form of obstructive breathing are associated with AD. During sleep, the apneic events consist of partial or complete closure of the upper respiratory airways leading to transient hypoxia. This, in turn, leads to intermittent brain arousals, increased oxidative stress and less clearance of toxic metabolites from the brain. Though comorbidities of cardiac arrhythmia and other cardiovascular problems are also linked to the development of AD, apnea is a major risk factor in developing AD. A recent meta-analysis reported that patients with AD have a 5% increased risk of presenting with obstructive sleep apnea in comparison to age-matched controls [23].

Depression

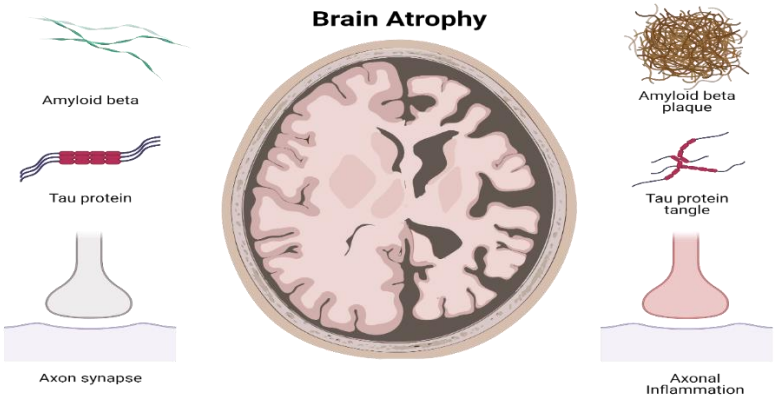
According to meta-analysis including both cohort and case control studies, depression plays a vital role along with other risk factors in the development of AD. A previous history of depressive episodes has a clear positive correlation to increased risk of developing AD [24].

Lower Educational Attainment

Lower educational attainment is thought to play a major role in defining cognitive impairment and the manifestation of late onset AD. It is speculated that higher cognitive development during early life can prevent the onset of AD and AD-related dementias. Although, non-AD dementias are influenced by lower educational attainment as other studies have shown. In 1994, a Canadian study showed that prevalence of AD is higher in persons with six or fewer years of formal education than those with ten years or more [25]. The "cognitive reserve model" suggests

ISSN-2767-5041

that intelligence might play a role in enhancing functioning of cognitive reserves, which can boost the neuronal synapses thereby slowing down the process of amyloid deposition. However, cognitive reserve is also affected by both genetic and environmental factors. Contrary to the cognitive reserve theory, there are other theories that the socioeconomical conditions of a country may play an important role in developing AD 26].



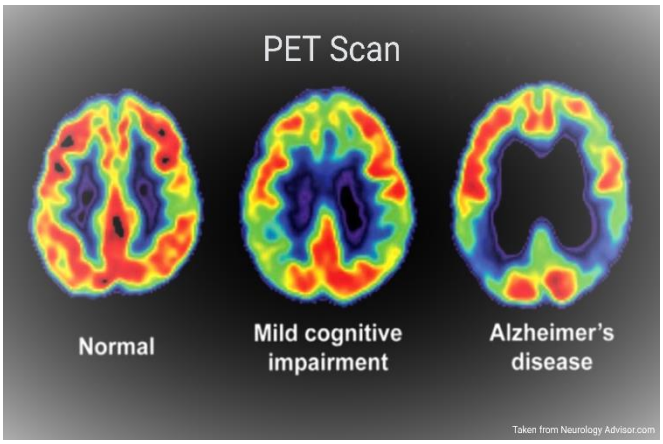
Diagnosis

The early diagnosis of AD is vital to seeking symptomatic prophylaxis. As the population is aging, AD is expected to surpass cardiovascular disease in disease-related deaths. AD is a complex neurodegenerative disease with clinical diagnoses ranging from mild cognitive impairment (MCI) to severe dementia according to National Institute on Aging–Alzheimer's Association (NIA–AA). A growing body of literature has shown that tau and amyloid plaques, while hallmarks of AD pathophysiology, do not fully describe the disease process. Neuronal and axonal inflammation as well as synaptic loss also contribute to the complexity of this disorder. All of foregoing neuropathies appear before any apparent cognitive decline in patients. Notwithstanding, scientists are discovering cerebrospinal fluid (CSF) and serum biomarkers as well as utilizing bioimaging techniques to aid to investigation of tau tangles and beta amyloid plaques in the brain and to differentiate it from other forms of dementia.

ISSN-2767-5041

Non-invasive diagnostic imaging

Positron Emission Tomography (PET) of the brain has been utilized to detect the beta amyloid peptides in plaque formation. There are radiolabeled tracers, including florbetapir, florbetaben



and flutemetamol to also detect amyloid plaque formations, but due to their costly nature and that most insurances will not cover the use of these tracers, it is often cost prohibitive for most patients and their families. Notwithstanding, it has been shown through autopsies that the technique exhibits 96% sensitivity and 100% specificity [27].

Utilizing iron oxide nanoparticles (NPs) or gold NPs as contrast agents or tagged with fluorescent probes to allow for rapid detection, magnetic resonance imaging (MRI) at increasing field strength and resolution may also be utilized for detection and identification of functional abnormalities in AD [28].

Evaluation of CSF

The examination of CSF for amyloid beta peptide, hyperphosphorylated tau (p-tau), total tau (T-tau) and neurofilament light protein (NFL) is an alternative, less costly option for the patients. Though invasive (lumbar puncture procedure), the diagnostic tool demonstrates 85-90% accuracy [29].

Evaluation of Serum

Serum biomarkers are used to detect circulating disease specific proteins in patients with AD. The method of diagnosis is less-invasive. A report by Shen *et al.* showed that for serum assays, the determination of BACE1 enzyme activity could discriminate individuals with normal

ISSN-2767-5041

cognition, MCI and dementia due to AD with sensitivity of 84% and specificity of 88%, though the study subjects was small in number [30]. Another study demonstrated that a panel of four serum miRNAs (including miR-31, miR-93, miR-143, and miR-146a) can serve as novel noninvasive biomarkers for AD diagnosis via RT-qPCR as these miRNAs participate in disease pathogenesis or progression [31]. With validation by future larger-scale studies, there is potential that a simple blood test may aid in the diagnosis of AD.

Therapy and management of Alzheimer's disease

There are currently five treatment options that are approved to treat the cognitive symptoms of AD in the United States, the last one being approved more than a decade ago. The European Union also has approved four of these five standard-of-care treatments which include three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and one N-methyl-D-aspartate receptor antagonist (memantine). In 2014, the fifth treatment option consisting of a combination dose of donepezil and memantine was approved in the United States for the treatment of patients with moderate to severe AD dementia who are already on stable donepezil therapy [32].

Interestingly, the nutraceutical huperzine A has proved beneficial in both improving memory function and daily activities. The use of huperzine A is not approved by the US Food and Drug Administration, though it is an approved medication in other countries. Another independent risk factor for the development of dementia is Vitamin D deficiency. Supplements are recommended for AD patients in whom deficiency is diagnosed.

ISSN-2767-5041

Finally, the management of cardiovascular risk factors contributes to overall brain health in both cerebrovascular and neurodegenerative diseases of any kind. Omega-3 fatty acid supplements including fish oil, which have specific cardiovascular benefits, have gained importance in studies and have proven to be effective in improving memory in AD patients. Adhering to particular dietary regimens, regular aerobic exercise, and recreational physical activities have proven to reduce the risk of developing cognitive decline and AD as well as reducing neuropsychiatric symptoms and increasing cognitive function in AD patients [27].

Future therapeutics

The current clinical research for treatment of AD involves targeting of the etiologic pathologies: neurofibrillary tangles (composed of p-tau) and amyloid plaques (extracellular) composed of amyloid beta (Aβ) protein. However, it is unclear which, if any, of the forgoing abnormalities is responsible for neurologic decline. Another strategy involves fortifying transcortical networks and enhancing inter-neuronal connections in order to improve cognitive function. Previous studies have already established that in order to slow or halt the progression of AD, early identification of the population at risk and subsequent treatment in the pre-clinical stage is of extreme importance. The current clinical trials are designed to recruit asymptomatic patients with a genetic predisposition or those who test positive for biomarkers that suggest increased risk of developing Alzheimer's dementia, with results expected early in the next decade. However, it is noteworthy that not even a single new agent has been approved for the treatment of AD since 2003 (memantine) notwithstanding several expensive and controversial drug development programs [27].

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Anti-amyloid

According to the amyloid hypothesis, toxic plaques are the earliest manifestation of AD. Subsequently, the formation of these plaques leads to all other pathologic and clinical findings, including tau-based NFTs, inflammatory damage, neuronal loss, vascular damage, and cognitive decline. Initial studies focused on increasing clearance of amyloid via two processes: first, active immunization with anti-amyloid vaccines and second by passive immunization with anti-amyloid antibodies (monoclonal). Two such monoclonal antibodies (bapineuzumab and solanezumab) which were initially developed in 2014 to remove these plaques from the brains of people with AD, not only failed to improve cognitive scores in patients with mild-to-moderate disease (mini-mental state examination, MMSE 16–26) but also failed to have a significant positive effect in patients with few to no symptoms (MMSE 20–26). Studies are still ongoing with similar drugs in this class, in an attempt to improve or preserve cognition in patients with mild cognitive impairment due to AD. Another approach to reduce Aβ plaque burden in the brain is by inhibiting either β- or γ-secretase enzymes that aid in the production of the Aβ peptide from its precursor, amyloid precursor protein (APP). Currently, several studies are ongoing to develop drugs which target β-site APP cleaving enzyme 1 (BACE1) as it is thought to be essential for the production of Aβ peptides. Though most of the studies have failed to yield any significant result in human trials, verubecestat, a novel drug, has recently demonstrated more than a 40-fold reduction in Aβ levels in the brains of rodents and primates, and it has shown a good safety profile in early human trials [33].

Anti-tau

The association of tau accumulation, both temporally and topographically, with cognitive decline is of critical importance in AD. This suggests that removal or prevention of accumulation of

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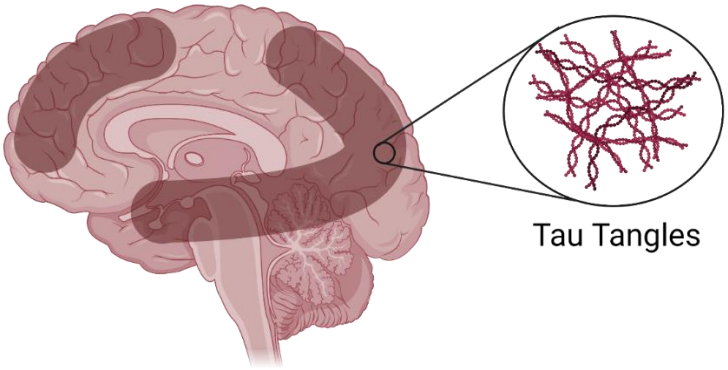
abnormal tau has a direct impact on the clinical manifestations of the disease.



Multiple tau vaccines have shown efficacy in animal models, and, in one recent study, an anti-tau vaccine, AADvac1, was found to be safe and stimulated a positive immune response in human subjects as well [34].

The major issue faced in the field of therapeutics against AD is the availability of drugs in the central nervous system. The blood-brain barrier (BBB) is the most obvious obstacle in the delivery of neurotherapeutic molecules (like drugs, peptides, etc.). Nanotechnology inclusive of nanoparticulate systems may be applied to overcome this problem thus reducing toxicity and improving therapeutic efficacy of the drugs. Though there are promising drugs against Aβ and tau, their maximum effect on the CNS cells cannot be evaluated without the application of nanoparticles to improve transfer of the drug across the BBB [28].

Neural Circuitry

The failure of several large scale clinical trials that targeted Aβ accumulation has led to the hypothesis that, even though the abnormal protein is implicated at the onset of AD, the progression of the clinical symptoms of the disease is caused by overall neural network dysfunction. Gamma oscillation, a high-frequency brainwave rhythm, has been implicated in inter-neuronal communication in virtually all brain networks and it aids in distinguishing

ISSN-2767-5041

between true and false memories. Recently, scientists at the Massachusetts Institute of Technology have reported that non-invasive induction of gamma-frequency oscillations resulted in reduced Aβ deposition and improved cognitive functions in the AD mouse model. This method is also currently in early phase clinical trials in humans, utilizing both visual and auditory stimulation [35].

The rise in prevalence and mortality of AD along with the growing total healthcare costs, necessitates the development of effective means for the early diagnosis and successful treatment of this progressive neurodegenerative disease.

Epidemiology

AD is the fifth major cause of death [36]. According to an estimate, 24 million people around the globe have dementia [37]. In the majority of patients, this dementia is related to Alzheimer's disease. A report from World Health Organization stated that in people over the age of 65, dementia is responsible for 11.2% of the total life in disability. This is more than cancer, cardiovascular disorders, and stroke. In 2005, Alzheimer's Disease International used the Delphi method to conclude that a total of 24.3 million people were suffering from dementia throughout the world in the year 2001 and by 2020 this number reach 42.3 million and it will further rise to 81.1 million by 2040 [37]. Experts from all over the world took part in this Delphi consensus.

AD is more common among women than men. At 45, men have 10% chances of developing AD, but women have a 20% chance. The reason can be in the genetics or overall higher life expectancy of women.

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Countries most affected by AD are China, the US, western Europe, and the developing countries from the western Pacific. It is evident that the chances of developing AD

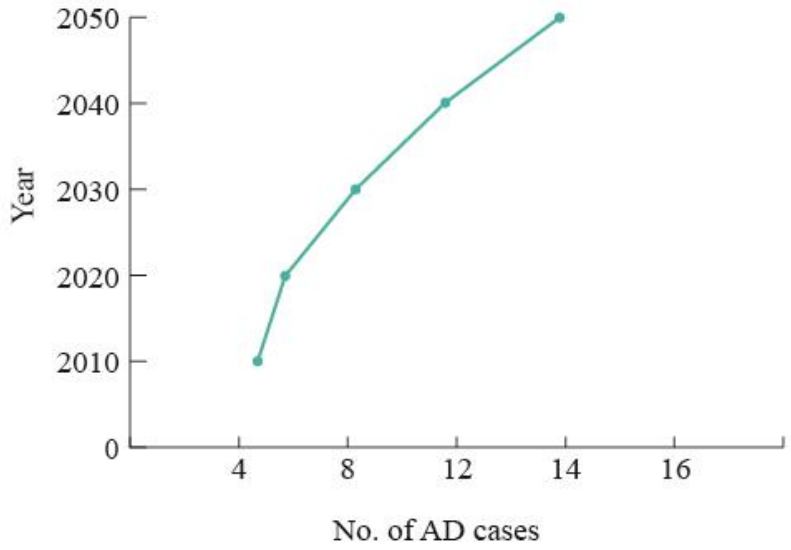


Figure IV: Graph showing the increase in number of patients (millions) over last two decades and projected cases for 2050 [38].

increase with age. Surprisingly, the chances of AD tend to decrease after 90 possibly due to hippocampal sclerosis.

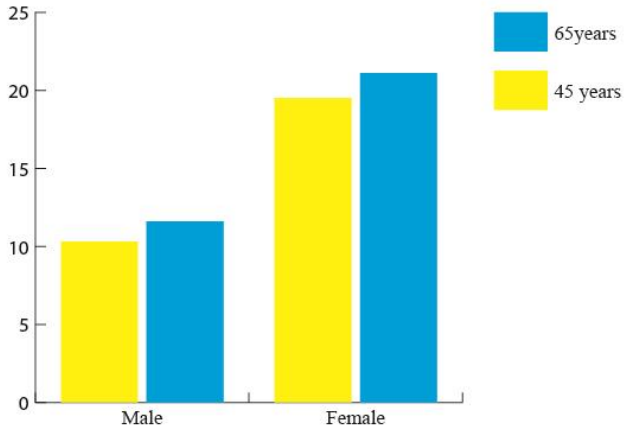
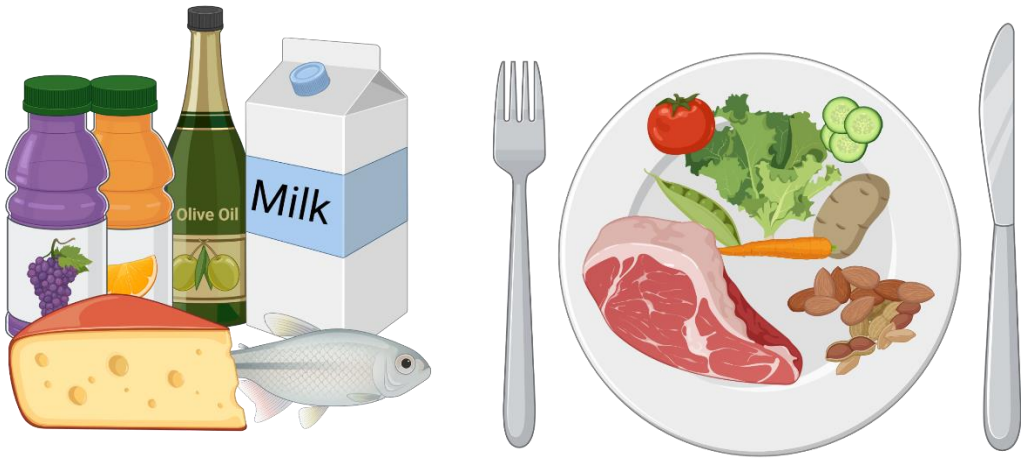


Figure V: Graph showing the comparison of incidence of AD in males and females [38].

ISSN-2767-5041

Prevention Through Diet

As in most diseases, the early diagnosis of dementia is key to stopping the spread of dementia and preventing it from developing into a disability. Previously the standard of detecting dementia was the development of advanced symptoms such as severe memory loss but developments in biomarkers and neuroimaging have led to early detection of changes in brain structure which can act as criteria for the diagnosis of dementia in the early stages. Certain diets have been considered as a preventive to AD.



Vitamin E

Tocotrienols (vitamin E) have antioxidant activity. Of the two types of tocotrienols, only alpha-tocopherol is present in brain. Studies have shown that AD patients have a low level of tocopherols and tocotrienols in their brain even before the onset of disease [39]. It is postulated that maintaining high levels of tocotrienols might be effective in preventing the onset of AD. Experiments on AD mice models revealed that oral dosing of vitamin E prevented oxidative stress thus providing protection against AD [39]. Taking Vitamin E orally contains only small amount of tocotrienols but due their high activity, this small amount is sufficient to produce antioxidant effects.

ISSN-2767-5041

TwendeeX

TwendeeX (TwX) has stronger antioxidant and anti-inflammatory activity than most vitamins. Due to its antioxidant activity, it was found to act against beta-amyloid and tau tangles pathology in AD mice models [39]. This leads to improvement in the cognitive functions of these mice. TwX contain coenzyme Q_{10}, niacin amide, L-cystine, ascorbic acid, succinic acid, fumaric acid, L-glutamine and riboflavin. TwX acts on the H_2O_2 metabolism to reduce the level of reactive oxygen species [39].

Ketogenic diet

AD patients can have impaired glucose metabolism as early as two decades before the onset of symptoms related to dementia. Although this can be used in the early diagnosis of AD. It also presents the opportunity of preventing AD if this impairment in glucose metabolism is avoided. Here ketone bodies can be effective, specifically beta-hydroxybutyrate and acetoacetate [40]. The brain can use these ketone bodies as an alternating source of energy to maintain its mitochondrial efficiency. Ketone bodies can also inhibit beta-amyloid production and can provide protection against their neurotoxicity [41]. A diet rich in ketone bodies not only prevents AD but can also reverse some of the damage caused by beta-amyloid to neurons. Trials by Henderson et al. measured the cognitive score of participants who were given a ketogenic compound called AC-1202. They found that the individuals having ApoE4 gene showed an increase in cognition [42].

Mediterranean diet

The traditional Mediterranean diet consists of high amount of fruits and vegetables, cereals, legumes, olive oil, nuts and seeds, and a moderate amount of fish, as well as a small amount of diary product and red meat. It is a balanced diet containing monounsaturated fatty acids, polyunsaturated fatty acids, antioxidants, vitamins (A, B1, 6, 9, 12, D, and E), and minerals.

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Evidence suggests that a Mediterranean diet can be effective in preventing dementia including AD. Studies have found that Americans on a Mediterranean diet had lower risk of AD [43].

DASH diet

The DASH diet is designed as a dietary approach to stop hypertension. It is rich in fruits, vegetables, nuts, whole cereal products, low-fat dairy products, fish, and poultry. These foods promote cardiovascular health by having blood pressure-reducing nutrients like potassium, calcium, "lean proteins," minerals, and fiber. The primary purpose of this diet is to protect against cardiovascular disorders, but it can also prevent AD due to its anti-inflammatory, antioxidant and insulin resistant actions[43]. However only a few studies have found positive results with regards to prevention of AD utilizing the DASH diet [43].

MIND diet

It is a hybrid of the Mediterranean diet and DASH diet. It contains 10 brain healthy foods and 5 unhealthy foods, all of them which are associated with the prevention of dementia. The brain healthy foods include: leafy green vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine while the unhealthy foods are: red meats, butter and stick margarines, cheese, pastries and sweets, and fried or fast food. All of the healthy foods were chosen due to their role in preventing AD. Separate studies on each of them have shown that they are beneficial in AD prevention [43].

While diet, exercise and currently available therapeutics will help ameliorate many of the symptoms associated with Alzheimer's Disease, advances in translational medicine offers the greatest hope for a potential cure to this devastating disease.

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