Review Article

A REVIEW ON ALZHEIMER'S DISEASE

Vineetha M[1*], Karunakar Hegde[1] and AR Shabaraya[2]

[1]Department of Pharmacology, Srinivas College of Pharmacy, Valachil, Post- Farangipete, Mangalore-574143, Karnataka, India.

[2]Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Post- Farangipete, Mangalore-574143, Karnataka, India.

ABSTRACT

Alzheimer's disease is the most common of the degenerative brain diseases and is characterized by impairment of cognitive function. Patients with this disorder lose the ability to encode new memories. Eventually, both declarative and non-declarative memory is significantly impaired, resulting in the capacity for reasoning, abstraction and language becoming progressively reduced. Alzheimer's disease and other dementias have devastating effects on families and caregivers, and is an increasing burden in an ageing society. It is estimated that 36 million people worldwide are living with dementia and this figure is expected to double every 20 years. Alzheimer's disease is the fourth leading cause of death in industrialized nations, preceded by cardiovascular disease, cancer and stroke. As yet there are currently no disease-modifying drugs approved to treat Alzheimer's disease. The therapeutics that are available only temporarily alleviate symptoms of cognitive impairment, however, they do not halt the inevitable progression of the disease. As such, major scientific efforts are underway in order to develop drugs which can help stabilize the disease. The publication of the "Amyloid Hypothesis" by Dennis Selkoe in 1991 helped to focus research efforts towards a causative protein involved in the disease, the amyloid β protein (Aβ). Aggregation and deposition of the Aβ protein is fundamental in the etiology of Alzheimer's disease and its importance has been demonstrated by a number familial heterogeneous mutations in the amyloid precursor protein that promote increased Aβ deposition, resulting in early onset phenotypes. There are several other aspects involved in disease progression such as neuro-inflammation and aberrant neuronal signaling, however, therapies targeting amyloid β aggregation have the potential to slow or even halt further neuro-degeneration and anti-Aβ therapies are regarded as a logical approach to treating Alzheimer's disease.

INTRODUCTION

Memory is special facility of brain which retains the events developed during the process of learning and both are mediated by nervous system[1]. Probably learning and memory are most evolutionary advantageous developments for human. Nootropics are the cognitive enhancers or nutraceuticals that are purported to improve mental functions, such as cognition, memory, intelligence, motivation and concentration, are also used for mental and learning deficit in children. Typically, nootropics are alleged to work by increasing the levels of neurochemicals in the brain[2].

Age, stress, emotions are conditions that may lead to memory loss, amnesia, anxiety, high blood pressure, dementia, or to more ominous threats like Schizophrenia and AD. Quality of life of senior citizens is adversely affected by dementia caused due to degeneration of the cerebral neurons[3].

Aging is a very complex process that alters an individual's normal functioning over a long period of time[4]. It involves deterioration of biological functions, especially brain and cognitive functions. However, this deterioration goes beyond what is expected from normal aging, it affects memory, intelligence, orientation, thinking, comprehension, learning capacity, judgment, calculation and language. This is what happens in individual's with Alzheimer's disease (AD). The condition worsens over the years, to the point that individuals affected by it experience physiological and behavioral changes. Dementia and AD are growing public health problem, with about 10 million new cases every year worldwide[5].

Alzheimer's disease is the most common type of dementia. "Dementia" is an umbrella term describing a variety of diseases and conditions that develop when nerve cells in the brain

(called neurons) die or no longer function normally. The death or malfunction of neurons causes changes in one's memory, behavior and ability to think clearly. In Alzheimer's disease, these brain changes eventually impair an individual's ability to carry out such basic bodily functions as walking and swallowing. Alzheimer's disease is ultimately fatal[6].

Within the past three years three cholinesterase inhibitors licensed (donepezil, rivastigmine and galantamine) have been licensed in the United Kingdom for use in mild to moderate Alzheimer ' s disease[7] Memantine is a NMDA receptor antagonist and is registered for the treatment of moderate to severe Alzheimer's disease[8].

ALZHEIMER'S DISEASE(AD)

Alzheimer's disease is a chronic, progressive neurodegenerative disease which is considered as the most common type of dementia among older people[9]. Its main manifestations are functional disorders of memory, intelligence, cognition, character, language and behavior in the elderly. At present, there is more than 36 million people who are currently estimated to have AD and this number is expected to be 118 million by the year 2050[10]. Approximately 5.3 million individuals in the United States are affected by Alzheimer's Disease (AD) . AD affects 4% of individuals over 65s and 20% of over 80s, with around 400 000 sufferers in the United Kingdom[11].

HISTORY OF DISEASE

The German psychiatrist and neuropathologist Dr.Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51-year-old woman with a 'peculiar disease of the cerebral cortex,' who had presented with progressive memory and language impairment, disorientation, behavioral symptoms (hallucinations, delusions, paranoia),and psycho social impairment[12]. Remarkably, many of the clinical observations and pathological findings that Alzheimer described more than a century ago continue to remain central to our understanding of AD today.

MAJOR SYMPTOMS OF ALZHEIMER'S DISEASE[13]

For doctors to make an initial diagnosis of Alzheimer's disease, they must first be satisfied that there is dementia - guidelines spell out what dementia consists of. It involves cognitive or behavioral symptoms that show a decline from previous levels of "functioning and performing" and interfere with ability "to function at work or at usual activities."

The cognitive decline is in at least **TWO** of the five symptom areas listed below (from guidelines jointly produced by the National Institute on Aging and the Alzheimer's Association)

1. Worsened ability to take in and remember new information, for example:

- Repetitive questions or conversations
- Misplacing personal belongings
- Forgetting events or appointments
- Getting lost on a familiar route.

2. Impairments to reasoning, complex tasking, exercising judgment:

- Poor understanding of safety risks
- Inability to manage finances
- Poor decision-making ability
- Inability to plan complex or sequential activities.

3. Impaired visuospatial abilities (for example, due to eye sight problems):

- Inability to recognize faces or common objects or to find objects in direct view
- Inability to operate simple implements, or orient clothing to the body."

4. Impaired speaking, reading and writing:

- Difficulty thinking of common words while speaking, hesitations
- Speech, spelling, and writing errors.

5. Changes in personality and behavior, for example:

- Out-of-character mood changes, including agitation; less interest, motivation or initiative; apathy; social withdrawal
- Loss of empathy
- Compulsive, obsessive or socially unacceptable behavior.

6. **Sleep patterns**: Normal sleep is a major problem in these types of patients. Many Alzheimer patients suffer from abnormal sleep patterns. They are wandering during the night around the berth place and sleeping during the day time. Normal sleep patterns are restored in the Alzheimer's patient by treating them with serotonin and dopamine optimization.

7. Restless Leg Syndrome: It is common and mostly contributed in creating the sleeping disturbance which leads to exacerbation of cognitive problems. With neurotransmitter optimization of serotonin and dopamine guided by neurotransmitter testing as indicted, Restless Leg Syndrome in the Alzheimer patient can be controlled.

8. Withdrawal from work or social activities: People with Alzheimer's may start to remove themselves from hobbies, social activities, work projects or sports. They may have trouble keeping up with a favorite sports team or remembering how to complete a favorite hobby. They may also avoid being social because of the changes they have experienced.

ASSOCIATED SYMPTOMS OF ALZHIEMER'S DISEASE

Apart from major symptoms, two symptoms are playing a vital role which is associated with Alzheimer's disease. The primary symptom of Alzheimer's disease is cognitive type of symptoms. They are Amnesia (short term and long term memory loss), aphasia, agnosia and apraxia. The secondary symptom of Alzheimer's disease is psychiatric type of symptoms. They are personality changes, depression, hallucinations and delusions.

PATHOLOGY OF ALZHEIMER'S DISEASE

A healthy adult brain has about 100 billion neurons, each with long, branching extensions. These extensions enable individual neurons to form connections with other neurons. At such connections, called synapses, information flows in tiny bursts of chemicals that are released by one neuron and detected by a receiving neuron. The brain contains about 100 trillion synapses. They allow signals to travel rapidly through the brain's neuronal circuits, creating the cellular basis of memories, thoughts, sensations, emotions, movements and skills.

Like all types of dementia, Alzheimer's is caused by brain cell death. It is a neurodegenerative disease, which means there is progressive brain cell death that happens over a course of time.

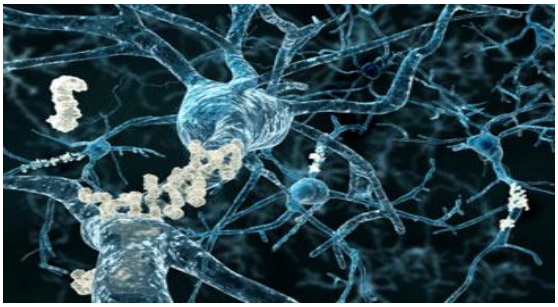

Fig. 1 : Neurons in Alzheimer's brain. there are microscopic 'plaques' and 'tangles' between and within brain cells

The total brain size shrinks with Alzheimer's - the tissue has progressively fewer nerve cells and connections[14].

At the cellular level, AD is characterized by a progressive loss of cortical neurons, especially pyramidal cells, that mediate higher cognitive functions Substantial evidence also suggests that AD causes synaptic dysfunction early in the disease process, disrupting communication within neural circuits important for memory and other cognitive functions. AD-related degeneration begins in the medial temporal lobe, specifically in the entorhinal cortex and hippocampus. Damage to these brain structures results in memory and learning deficits that are classically observed with early clinical manifestations of AD[15].

There are 3 consistent neuro pathological hallmarks:

- Amyloid-rich senile plaques –Amyloid hypothesis
- Neuro fibrillary tangles –TAU hypothesis
- Neuronal degeneration

These changes eventually lead to clinical symptoms, but they begin years before the onset of symptoms.

1) **Amyloid Hypothesis:** Amyloid precursor protein (APP) is the precursor to amyloid plaque. APP sticks through the neuronal membrane. But some enzymes (Chaperone enzymes) cut the APP into fragments of protein, including beta-amyloid. β- Amyloid fragments come together in clumps to form senile plaques in substantianigra. These clumps disrupt the work of neurons that affects the hippocampus and other areas of the cerebral cortex.

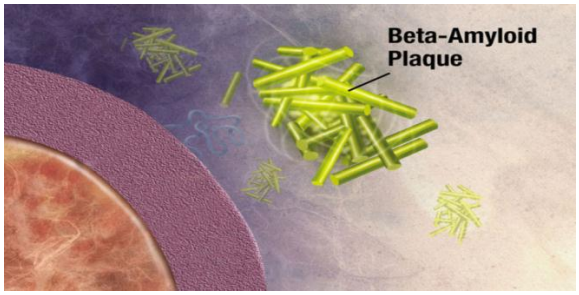

Fig. 2 : Beta-Amyloid Plaque

2) **Tau hypothesis**;- Neurons have an internal support structure partly made up of Microtubules**.** A protein called tau helps to stabilize these microtubules. This hypothesis claims that threads of tau protein twist and tangle together, which leads to Alzheimer's disease. When tangles formed inside the bodies of nerve cells, the microtubules disintegrate , destroying the structure of the cells. Which leads to collapse of the support and transportation system. This causes interference and malfunction in the communication between neurons and later it leads to brain cell death.

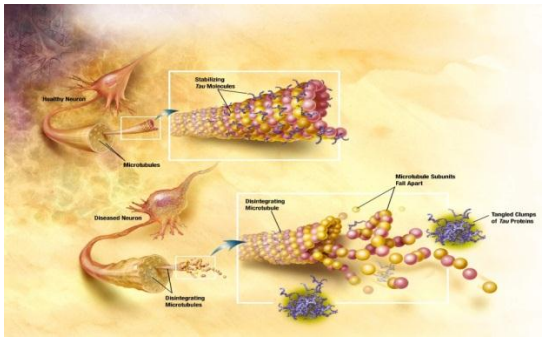

Fig. 3: Development of neurofibrillary tangles

3) **Cholinergic hypothesis:** It states that Alzheimer's begins as a deficiency in the production of cholinergic neurotransmitter acetylcholine, as a potential causative agent for the formation of plaques and tangles in cortical regions leading to generalized neuroinflammation[16].

VARIOUS STAGESS OF ALZHEIMER'S DISEASE

STAGE-I (Pre-Dementia):-A mild cognitive symptom which occurs in the initial stage within 2 months and is observed by the following actions such as attentiveness, planning, abstract thinking and semantic memory.

STAGE-II (Early – Dementia):-This mild stage, which usually lasts 2 to 4 years. In this stage, family and friends may begin to realize that there has been a decline in the patient's cognitive ability. Common symptoms at this stage include;-

- Difficulty retaining new information
- Difficulty with problem solving or decision making. Patients may start to have trouble
- managing finances or other instrumental activities of daily living.
- Personality changes. The person may begin to withdraw socially or show lack of motivation.
- Difficulty expressing thoughts
- Misplacing belongings or getting lost. The patient may have difficulty navigating in familiar surroundings.

Stage-III (Moderate Dementia);-Lasting 2 to 10 years, this is longest stage of the disease. Patients often experience increased difficulty with memory and may need help with activities of daily living. Symptoms frequently reported during this stage include;-

- Increasingly poor judgment and confusion. The patient may begin to confuse family members, lose orientation to time and place, and may begin wandering, making it unsafe for them to be left alone.
- Difficulty completing complex tasks, including many of the instrumental activities of daily living, such as managing finances, grocery shopping, planning, and organization.
- Greater memory loss. Patients may begin to forget details of their personal history.
- Significant personality changes. The person may become withdrawn from social interactions and develop unusually high suspicions of caregivers.

Stage-IV (Advanced Dementia);- In this final stage of the disease, cognitive capacity continues to decline and physical ability is severely impacted. This is a complete stage for a period above 10 years and is completely dependence on care givers. It is the mature stage of the disease. Common symptoms

appearing in this stage include;-

- Loss of ability to communicate. The patient may still speak short phrases, but are unable to carry on a coherent conversation.
- Reliance on others for personal care, such as eating, bathing, dressing, and toileting. Many patients become incontinent.
- Inability to function physically. The person may be unable to walk or sit independently.
- Muscles may become rigid and swallowing can eventually be impaired.

DIAGNOSIS

It is very important to get an early and accurate diagnosis of Alzheimer's disease in order to effectively treat it as early as possible. These herbal treatments should begin (along with regular brain exercises) immediately after diagnosis to maximize the potential of leading a normal and healthy life. Alzheimer's disease can be reliably diagnosed with a complete examination that includes the following tests:

- A complete medical and psychiatric history
- A neurological examination
- Laboratory tests to rule out anemia, vitamin deficiencies, and other conditions
- A mental status examination to evaluate the person's thinking and memory
- Talking with family members or caregivers
- Mental Status Examination Diagnostic tests for Alzheimer's Disease: One of the key diagnostic tests for dementias such as Alzheimer's is the Mental Status Examination (MSE).
- The Mini-Cog test takes about three minutes to administer and is often used in Emergency Departments, for people who appear to have some type of dementia like Alzheimer's disease.
- Urinalysis Urine test:
- Routine analysis of urine is just one of the tests that your doctor will do if Alzheimer's disease or another type of dementia is suspected. Urinalysis (urine tests) screens for abnormalities. Urinalysis can detect a number of diseases or conditions where symptoms may be similar to dementias such as severe renal disease.
- Mild Cognitive Impairment (MCI)
- People may sometimes fear the onset of dementia, whereas, they will be experiencing mild cognitive impairment.
- Visual Clues to Dementia Diagnosis
- There are a number of strong visual clues that can indicate that someone may be suffering from a dementia such as Alzheimer's disease. Appearance, dress, and personal hygiene may deteriorate. Visual clues are important, but provide only one aspect of human behavior and presentation that may lead to diagnosis.
- Lumbar Puncture test
- Although uncommon in tests of dementia the lumbar puncture can reveal rare diseases that can mimic the signs of dementia
- The Mini Mental State Examination (MMSE) is most commonly used to test for memory problems and contributes to a possible diagnosis of dementia.
- The electroencephalogram (EEG) is a useful tool in the diagnosis of Alzheimer's. Those with the disease have a diffuse and symmetrical slowing of the brain waves that register on the EEG[17].

Epidermiology and Risk factors

Alzheimer's disease is estimated to affect nearly 15 million people worldwide. New cases increase steadily from 0.5% per year at age 65 years to about 8% per year after age 85 years. Because the survival rate of disease is quite high, the prevalence also increases from 3% at age 65 years to nearly 40% after age 85 years. Aging is the greatest risk factor for AD, and most people affected by the disease are older than 65 years. However, although aging is the strongest known risk factor, AD is not an inevitable consequence of aging. In fact, about 9% of cases happens before the age of 65 years and are classified as early onsets of AD.

In terms of risk factors, some studies have shown a relationship between the development of AD and other lifestyle factors present in most non-communicable diseases. Shared risk factors are thought to be physical inactivity, obesity, unhealthy diets, tobacco use and harmful use of alcohol, diabetes, hypertension, and heart disease. Yet, evidence for these relationships is not homogeneous, and further studies are needed to establish a clear connection between specific lifestyle related risk factors and the development of AD[33c].

In terms of genetics, individuals who had a first-degree relative affected by AD seem to be more likely to develop the disease. The *APOE* gene is thought to be involved in this process.one form of this gene *APOEε4,* increases a person's risk of developing the disease and also associated with an earlier age of onset. However, carrying the gene does not necessarily mean developing the disease.

In fact, most genetic mechanisms of AD among families has yet remained largely unexplained. Finally, people with Down syndrome are more likely to develop the disease, which usually happens earlier than for most patients with AD.

Additional potentially modifiable risk factors include depression, low educational attainment, social isolation, and cognitive inactivity.

In addition, people who have had a severe head trauma or head injury seem to have a greater risk of AD. Finally, women seem to be more likely to develop AD, although this might also be because of the fact that women generally live longer than men.

The dys regulation of bio metal (Cu, Zn, Fe) homeostasis and oxidative stress in the brain cells are major hallmarks in the pathogenesis of Alzheimer's disease (AD). During the 1960s and 1970s, aluminum emerged as a possible suspect in causing Alzheimer's disease. This suspicion led to concerns about everyday exposure to aluminum through sources such as cooking pots, foil, beverage cans, antacids, and antiperspirants. Since then, studies have failed to confirm any role for aluminum in causing Alzheimer's, but few experts believe that continuous exposure to aluminum source may cause threat[18].

CURRENT TREATMENT FOR ALZHEIMER'S DISEASE

NONPHARMACOLOGIC TREATMENT

- Cognitive enhancement therapy
- Individual and group therapy
- Regular appointments
- Communication with family, caregivers
- Environmental modification
- Attention to safety

PHARMACOLOGIC TREATMENT:

1 CHOLINERGIC ACTIVATORS: Tacrine, Donepezil, Rivastigmine, and Galantamine are the drugs used to treat Alzheimer's disease act by inhibiting acetylcholinesterase activity.

These drugs block the esterase-mediated metabolism of acetylcholine to choline and acetate This results in Increased acetylcholine in the synaptic cleft thus Increased availability of acetylcholine for postsynaptic and presynaptic nicotinic (and muscarinic) acetylcholine receptors. Tacrine is an anticholinergic drug which inhibits both acetyl cholinesterase and butyryl cholinesterase enzymes which inhibits the effects promoted by M1 and M2 cholinoceptors. Velnacrine, a cholinomimetic analog of tacrine is currently under investigation. Donepezil49 is another acetyl cholinesterase inhibitor which is presently available.

2. N-METHYL-D-ASPARTATE (NMDA) PATHWAY DEGENERATION: Over stimulation of N-methyl-D-Aspartate (NMDA) produces excitotoxic effects on neurons which further produces neurodegenerative processes. This problem is overcome by treatment with amantadine derivatives such as Memantine (dimethyl adamantine) which is an uncompetitive inhibitor of NMDA receptors.

3. IMMUNO THERAPY: Both active (vaccination) and passive (monoclonal antibodies) immunization are studied in AD patients after promising data from in vitro experiments and animal studies. Active immunization against Aβ42 in transgenic mice resulted in decreased plaques and improved cognitive function.

4. ESTROGEN THERAPY:

Estrogens are neuroprotective against oxidative stress, excitatory neurotoxicity, and ischemia in the brain. Studies shown that estradiol administration significantly ameliorates the neurodegeneration characteristic of AD in experimental rat model. This may be attributed to its powerful antioxidant, antiapoptotic, neurotrophic as well as its antiamyloidogenic activities.

5. HMG-COA REDUCTASE INHIBITORS (THE "STATINS"): Epidemiologic studies indicated reduced AD prevalence in individuals who take statins. In vitro studies showed that cholesterol-rich diet increased β-secretase processing of APP while cholesterol lowering resulted in decreased Aβ production.

The view that increased levels of cholesterol facilitate Aβ production while statins treatment lowers Aβ production led to the hypothesis that statins may be a promising treatment for AD. Clinical trial with atorvastatin for 1 year provides some clinical benefit in AD patients.

6. MONOAMINE OXIDASE INHIBITORS: MAO inhibitor deprenyl is an anti-Parkinson drug used to inhibit dopamine degradation in the brain. Also as a neuroprotective agent, deprenyl has been used to slow the progress of neurodegenerative diseases such as AD for many years. Although controversial, some clinical trials have indicated that deprenyl could alleviate some symptoms of AD.

7. AB-AGGREGATION INHIBITORS: The neurotoxic effect of Aβ has been documented on numerous occasions and thus decreasing its neurotoxicity or inhibiting its aggregation may have therapeutic potentials. The first drug was a β-sheet breaker iAβ5p, which showed that in hippocampal injection of it resulted in improved spatial memory and decreased amyloid plaque deposits[19].

CONCLUSION

Since Alois Alzheimer described the first case of AD more than a century ago, much progress has been made in understanding the biology and clinical aspects of the disease. Alzheimer's disease(AD)is a complex, multifactorial, heterogeneous mental illness. In light of the pathogenic complexities of AD, it is probably unlikely that single-target drugs will achieve satisfactory curative effects. So, the treatment of AD remains a challenge in the modern medicine and current therapeutic modalities cannot successfully halt the progression of AD at a nearly stage.

The present review reveals about the history, Etiology, Pathogenesis and current treatments about Alzheimer's disease. There is no cure for AD, and drug therapy for the disease is still in its infancy. Approved medications for the treatment of probable AD help control the symptoms of AD but do not slow down the progression or reverse the course of the disease itself.

REFERENCES

1. Chatterjee CC. Human physiology, 1st edition, Medical Allied Agency Calcutta.1997;5(2);264.
2. Shymal K, Sandip pal, Malay K. Ghosal. Dementia Indian Scenario, Neural India 2012;60(6);618-624.
3. Kaufer DI Cummings, JL Christine D, Geriatr psychiatry Neurol. Effect of tacrine on behavioral symptoms in Alzheimer's disease; an open-label study.1996;91-6.crossref
4. Queen BL; Tolletsbol TO. Polyphenols and aging. Curr Aging Sci. 2010;3:34-42.
5. Dementia (online). World Health Organization (cited 5 January 2018).
6. Alzheimer's Association 2013. Alzheimer's disease facts and figures, PDF document. accessed November 1st, 2013.
7. Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, Perry RH. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. BMJ 1978, (ii): 14579.
8. S.K. Sonkusare, C.L. Kaul, P. Ramarao. Dementia of Alzheimer's disease and other neurodegenerative disorders-memantine, a new hope Pharmacol Res, 51(2005),pp. 1-17.
9. Solomon, M. Kivipelto, and H. Soininen, "Prevention of Alzheimer's disease moving backward through the life span", Journal of Alzheimer's Diseases, vol.33, Supplement 1, pp.465-469,2013.
10. Y. Huang and L. Mucke, "Alzheimer mechanism and therapies no.6, pp.1204, 2012.
11. Cognitive function and dementia in 6 areas of England and Wales: the distribution of MMSE and prevalence of GMS organicity level in the MRC CFA study. The Medical Research council Cognitive Function and Ageing Study(MRC CFAS). Psychol Med 1998;28:319-35.
12. Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. Lancet 1997;349(9064):1546-9. doi: 10.1016 150140-6736(96)10203-8.
13. McKhann GM, Knopman DS, Chertkow H. the diagnosis of dementia due to Alzheimer's disease: Recommendation from the National Institute of Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.2011,7(3);263-269.
14. Norfray JF, Prorenzale JM. Alzheimer's disease: neuro-pathologic findings and recent advances in imaging. AJR Am J Roentgenol 2004; 182:3-13.
15. Lane CA, Hardey J, Schott JM. Alzheimer's disease. Eur J Neurol 2018;25:59-70.
16. Shen ZX(2004). "Brain cholinesterase II. The Molecular and Cellular basis of

Alzheimer's disease". Med hypothesis 63(2):308-21.
17. Kuller L.H. Hormone replacement therapy and its relationship to dementia. J Am geriatr soc.1996;44:878-80.
18. Shin RW. Interaction of aluminium with paired helical tau involved in neurofibrillary pathology of Alzheimer's diseases. Cold spring Harb Perspect Med.2012;2,a006339.
19. Hyman BT, Phelps CH, Beach TG, and others. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease, Alzheimer's and Dementia. The Journal of the Alzheimer's Association .2012;8(1);1-13.