Alzheimer's: An Update Based on Clinical Science

Shivani P, Altaf M, NagaVamSidhar M, Qadrie Z

INTRODUCTION
Alzheimer's disease is a chronic neurodegenerative disorder that progresses gradually affecting cognition and behavior earliest symptom is short term memory loss. With the progression of the disease, symptoms include mood swings, disorientation, problem with language, loss of motivation, behavioral issues. Gradually losing the body functions which ultimately lead to death. In the year 2015, 1.9 million Deaths resulted due to dementia. The most common cause of Alzheimer's disease is the combination of genetic, environmental factors and lifestyle that affects the brain over time. 5% of the Alzheimer’s disease is caused by specific genetic changes which will develop the disease. Alzheimer's disease is caused by brain cell death. In Alzheimer’s disease the total brain size reduces and the nerve cells, connections progressively decrease in the brain. The brain affected with Alzheimer’s disease cannot be seen or tested in living conditions but, the small inclusions in the nerve tissue called plaques and tangles are shown in postmortem/autopsy. With the progress of Alzheimer's disease to its last stages changes in the brain starts to affect physical functions such as swallowing bowel and bladder control and balance.

Key Words: Alzheimer’s Disease, Neurodegenerative Disorder, Dementia, Autopsy.

ABSTRACT
Alois Alzheimer, a German psychiatrist and pathologist characterized Alzheimer's disease in 1907; chronic neurodegenerative disorder that progresses gradually affecting cognition and behavior earliest symptom is short term memory loss. With the progression of the disease, symptoms include mood swings, disorientation, problem with language, loss of motivation, behavioral issues. Gradually losing the body functions which ultimately lead to death. In the year 2015, 1.9 million Deaths resulted due to dementia. The most common cause of Alzheimer's disease is the combination of genetic, environmental factors and lifestyle that affects the brain over time. 5% of the Alzheimer’s disease is caused by specific genetic changes which will develop the disease. Alzheimer's disease is caused by brain cell death. In Alzheimer’s disease the total brain size reduces and the nerve cells, connections progressively decrease in the brain. The brain affected with Alzheimer’s disease cannot be seen or tested in living conditions but, the small inclusions in the nerve tissue called plaques and tangles are shown in postmortem/autopsy. With the progress of Alzheimer's disease to its last stages changes in the brain starts to affect physical functions such as swallowing bowel and bladder control and balance.

INTRODUCTION
Alzheimer's disease is a chronic neurodegenerative disorder that progresses gradually affecting cognition and behavior(1, 2). In 1907, Alois Alzheimer, a German psychiatrist and pathologist characterized Alzheimer's disease (3). 60-70% cases of dementia are caused by Alzheimer's disease (1, 2). 100 years back Alzheimer’s disease was identified but 70 years back it was identified as commonest cause of dementia and even major cause of death (4). The usual onset of the Alzheimer's disease is over 65 years of age (5). In 2015, worldwide approximately 29.8 million people were affected with Alzheimer’s disease (6, 2). The earliest symptom is short term memory loss (1). With the progression of the disease, symptoms include mood swings, disorientation, problem with language, loss of motivation, behavioral issues (1, 2). Gradually losing the body functions which ultimately lead to death (7). 1.9 million Deaths resulted due to dementia in 2015 (8). The main path physiologic mechanism causing Alzheimer's disease was not known properly and no treatment for Alzheimer’s disease (9). Alzheimer's disease appears to be frightening, mysterious and daunting (10). There are still a lot of unknown reasons about Alzheimer’s disease which anguish more than 5 million Americans (10). Mainly neurons get affected with Alzheimer’s disease. After neurons get damaged and destroyed, affects the other parts of the brain including those of normal body functions such as walking, swallowing and Alzheimer's disease is major cause of dementia (11, 12). The main risk factors include genetic, head injuries, depression, and hypertension (1, 13). The process of the disease associates with tangles and plaques in the brain (13). Following diagnosis, the average life expectancy will be about 3-9 years (7, 14). There are about 100 billions of neurons with long extensions in the adult healthy brain. And 100 trillion synapses are present in the brain. Signals from the synapses travel through the brain neuronal circuits. Beta amyloidal protein (called Beta -amyloidal plaques) is accumulated outside the neurons and the tau protein (called tau tangles) accumulates inside the neurons which ultimately lead to Alzheimer’s disease and other symptoms (15, 16).

STAGES OF ALZHEIMER'S DISEASE:
Experts have documented common patterns of symptom progression that occurs in many individuals with Alzheimer's disease and developed several methods of "staging" based on these patterns (17).

STAGE 1: No Cognitive Impairment
Individuals will have no health problems and no evidence for health care professionals during medical interview.

STAGE 2: Very Mild Decline
At this stage individuals experience memory lapses, mainly forgetting familiar names, their everyday needs, keys, eye glasses but it is not evident for health care professionals or friends, family (17).

STAGE 3: Mild Cognitive Decline
Only in some cases, early stage alzheimers can be diagnosed. At this stage all the family members, friends etc., start identifying the problem. The memory problem can be measured by medical testing and through detailed medical interview. Common problems include:

- Forgetting familiar names
- Loosing valuable objects
- Decrease in the ability to plan.

STAGE 4: Moderate Cognitive Decline (mild or early stage Alzheimer’s disease)
This is the stage where a medical interview detects the problems in the following areas:

- Loss of knowledge of recent and current events
- Declined capacity to do difficult tasks such as planning dinner for guests, paying bills and Managing finances, marketing.
- Decreased memory of personal history.

STAGE 5: Moderately Severe Cognitive Decline (moderate or mild stage Alzheimer’s)
Significant gaps in memory and deficiency in cognitive function emerge.Individuals faces difficulty throughout the medical interview to recall about his important details like mobile number, address, name of the college or school from which they got graduated. Conventionally requires no aid with eating and using...
the toilet. Selecting nice clothing for the event or season is needed.

STAGE 6: Severe Cognitive Decline (Moderately severe or mild stage Alzheimer's disease)

Worsening of memory difficulties continue to carry out the daily activities of the affected individual. Increased episodes of fecal incontinence and urine. Normal sleep/ wake cycle gets disrupted. And personal history cannot be recollected properly. Changes in personality and behavioral symptoms like delusions, hallucinations, repetitive behavior or compulsive.

STAGE 7: Very Severe Cognitive Decline (Severe or late stage Alzheimer’s disease)

This is the end stage of the disease where the ability to respond to their environment is completely lost such as ability to speak, and control movement (17).

ETIOLOGY

The most common cause of Alzheimer’s disease is the combination of genetic, environmental factors and lifestyle that affects the brain over time. 5% of the Alzheimer’s disease is caused by specific genetic changes which will develop the disease (18). Alzheimer’s disease is caused by brain cell death (19). In Alzheimer’s disease the total brain size reduces and the nerve cells, connections progressively decrease in the tissue (19, 20). The brain affected with Alzheimer’s disease cannot be seen or tested in living conditions but, the small inclusions in the nerve tissue called plaques and tangles are shown in postmortem / autopsy (19,20). The risk of the Alzheimer’s disease and other symptoms is increased by heart and vascular problems including: Diabetes, High blood pressure and Stoke (10)When Alzheimer’s brain was examined under microscope by the doctors, two types of abnormalities are visible:

A. Plaques: Beta amyloidal protein forms clumps and destructs and damage the brain cells through interfering with cell to cell communication.

B. Tangles: For carrying nutrients to the brain cells supporting and transporting systems are needed. A protein called “tau” is necessary for the functioning of supporting system. The transporting system is failed in Alzheimer’s disease due to, as the tau protein threads twists into abnormal tangles inside the brain cells (18).

EPIDEMIOLOGY

In United States 2016, ages of people with Alzheimer’s disease are (21)

<table>
<thead>
<tr>
<th>AGE</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>85+ years</td>
<td>3%</td>
</tr>
<tr>
<td>75-84 years</td>
<td>44%</td>
</tr>
<tr>
<td>65-74 years</td>
<td>15%</td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>4%</td>
</tr>
</tbody>
</table>

In 2016, 5.4 million Americans of all ages have Alzheimer’s disease. Among the 5.4 million people are 65 years and older in age (22) and approximately 200,000 individuals have early onset of Alzheimer’s below 65years (23).

At 65years and older, one in nine people (11%) has Alzheimer’s disease. At 85 years and older, one third of people has AD (21). At 75years or older age, 81% of people have AD (21).

By 2025, people at 65 years or older with AD are estimated to reach 7.1 million that is, there is 40% rise from 5.2 million at 65 years or older age affected in 2016 (21). By 2050, the population with AD at 65years or older becomes triple from 5.2 million to 13.8 million. By 2020, approximately 7% of world population at age 60 years or above will be living in developing countries and 14.2% in India (24).

According to the estimation, currently 44million people with AD dementia exist in this world and by 2050, the population grows more than 100 million cases (25, 26).

RISK FACTORS:

The risk factors for Alzheimer’s disease are Age, Family history and genetics .Down, syndrome, Sex , Mild cognitive impairment ,Past head trauma and Lifestyle and heart health

Age: Greatest risk factor for Alzheimer’s disease is increasing age. After 65years the risk increases (27).

Genetics: Risk of developing Alzheimer’s disease is more with first degree relatives when your parents or siblings have the disease. Most genetic mechanism of Alzheimer’s among families is mostly unexplained. The main risk gene present is apolipoprotein e4 (APOE4), even everyone with gene does not develop Alzheimer’s disease. Mutations involve the gene for the Presenilin 1 and Presenilin 2 proteins (27). 95% chance of developing the Alzheimer’s disease is due to inheriting a mutation into Persenilin 2 gene (28).

Down Syndrome:

An additional full or partial copy of chromosome 21, in one of the 23 human chromosomes is present in Down syndrome patients. People above 65 years ago with Down syndrome will develop Alzheimer’s disease (29, 30). In people with Down syndrome, signs and symptoms of Alzheimer’s disease appears 10-20 years early (27).

Sex

Women have the chance to develop Alzheimer’s disease more than men as, they live longer.

Mild Cognitive Impairment (MCI)

People with MCI will have defects in memory, and also have an increased risk but not certainly of lasted developing dementia (27).

Post Head Trauma

People with severe head trauma may have a greater risk of developing Alzheimer’s disease.

Life Style And Heart Health

Some evidence says that the risk factors which develop the heart diseases also may increase chance of developing Alzheimer’s disease.

Examples include: High blood cholesterol, Obesity, Lack of exercise, Smoking or exposure to second hand smoke, High blood pressure, and diet lacking in fruits and vegetables

These risk factors are associated to vascular dementia a type of dementia caused by damaged blood vessel in brain (27).

Complications

With the progress of Alzheimer’s disease to its last stages changes in the brain starts to affect physical functions, such as swallowing, bowel and bladder control and balance (27).

Other complications include:

a) Fractures
b) Pneumonia and other infections
c) Bedsores
d) Inhaling food or liquid into lungs (aspiration)
e) Malnutrition or dehydration (27)

SIGNS AND SYMPTOMS

The main symptom of AD is memory loss (31). And people may experience:

- Cognitive: difficulty in thinking, mental confusion, delusions, disorientation, forgetfulness, inability to do simple moths and mental decline.
- Behavioral: personality changes, lack of restraint, difficulty with self-care, aggression, agitation and irritability.
• Mood: Mood swings, general discontent, anger, apathy and loneliness.
• Psychological: hallucinations, depression, paranoia.

Symptoms based on stages of AD:(32)

<table>
<thead>
<tr>
<th>Mild AD</th>
<th>Moderate AD</th>
<th>Severe AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of spontaneity and sense of initiative</td>
<td>Hallucinations, delusions and paranoia</td>
<td>* AD is often diagnosed at this age</td>
</tr>
<tr>
<td>Poor judgment loading to bad decisions</td>
<td>Difficulty with language</td>
<td>-</td>
</tr>
<tr>
<td>Memory loss, Repeating questions and Losing things or misplacing them in odd place.</td>
<td>Increased memory loss and confusion</td>
<td>Difficult in swallowing and Skin infections</td>
</tr>
<tr>
<td>Wandering and getting lost</td>
<td>Difficulty carrying out multi step tasks, such as getting dressed</td>
<td>Difficulty in swallowing and Skin infections</td>
</tr>
<tr>
<td>Mood and personality changes</td>
<td>Agitation, anxiety, tearfulness, restlessness</td>
<td>* At this stage people with AD cannot communicate and depends completely on others. At the end most of the people may <strong>on bed as the body shut down</strong></td>
</tr>
</tbody>
</table>

PATHOPHYSIOLOGY

The exact mechanism of Alzheimer's disease is not clearly known. It is understood based on the hypothesis.

There are about 4 hypotheses:

1. **Amyloid Hypothesis** AB protein is largely present in the cortical plaques of Alzheimer's disease brains. AB protein is produced through formation of its parent protein, App (33). The gene encoding for App lies present on chromosome 21. The specific physiological roles of App are not completely clear but in general, it is useful to maintain proper neuronal function and perhaps cerebral development (34). As plaques consists AB protein and patients with Down syndrome has trilogy 21, both perhaps cerebral development (34).

In 1991, a family with autosomal dominant exposed an App gene mutation (35). Immediately after this, the amyloid cascade hypothesis was formulated. In its original form, the amyloid cascade hypothesis proposed a change in App processing with their base line (33). The following diagnosis is often done by health care provider to diagnose AD are:

* Tests done to know other possible causes of dementia are:
  - **Complete physical examination, including neurological exam**
  - **Asking questions about medical history and symptoms.**
  - **Mental status examination or cognitive tests (53).**

These ions affect and are affected by App, tau and APOE (46) and their deregulation may cause oxidative stress that may contribute to pathology (47, 48, 49, 50, 51).

2. **Cholinergic Hypothesis** Based on the currently available drug therapy, cholinergic hypothesis (37) proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. As the cholinergic hypothesis has no widespread support, because of the medications which are used to treat acetylcholine deficiency have not been very effective (38). In toxification from medication

3. **Tau Hypothesis** Based on the Tau hypothesis, tau protein abnormalities initiate the disease cascade (41). In this hypothesis, hyperphosphorylated tau starts to pair with other threads of tau, which forms neurofibrillary tangles inside the nerve cell bodies (43). When these neurofibrillary tangles occur, the microtubules disintegrate, destroying the structures of the cell, cytoskeleton which collapses the neurons transport system (43). This may first lead to malfunctions in the biochemistry communications between neurons and later causing death of the cells (44).

4. **Other Hypothesis** Poor functioning of blood brain barrier may be involved in neurovascular hypothesis (45). In AD, the cellular homeostasis of bimetallic such as iron, copper, zinc and iron are disrupted though; it remains unclear whether this is caused by the changes in the proteins.

To rule out the other causes of dementia such as brain tumors or stroke, computed tomography (CT) or Magnetic resonance imaging (MRI) are done. The brain image scans may bra normal during the early stages of dementia but later on stages, MRI may show a decrease in the size of different areas of brain (53). When the scans donor confirms the diagnosis of AD, they exclude other dementia causes such as stroke and brain tumors (53). To diagnose other cerebral pathology or subtypes of dementia, single - photon emission computed tomography (SPECT) or Positron emission tomography (PET) are used (54), it also predicts the conversion from prodromal stages(mild cognitive impairment) to AD (55).

TREATMENT

Non - Pharmacological treatment

Non - pharmacological treatment is important part in treating AD. The main non - pharmacological treatment includes: educating patients about the disease, prognosis and life style changes (3).

Life style changes includes

Physical activity Regular physical exercises onset of dementia by sustained cerebral perfusion (56). Recently Colombes and Kramer (57) showed that physical fitness decreases the loss of hippocampus brain tissue in aged brain.
Cognitive activities, leisure activities and socialization:

Intellectually challenging activity of various types has been associated with a reduced risk of dementia in longitudinal studies (58,59,60,61,62,63,64,65). Doing complicated activities like reading books or newspaper, to write for pleasure, doing Crossword puzzles, playing board games.

Diet

With strong epidemiologic evidence, along with physical inactivity, poor diet is most leading cause for deaths for Americans (66). Bioactive compounds like antioxidants mainly present in fruits and Vegetables are important for protection against nitrosamine and oxidative stress (66).

Pharmacological Treatment

Actually, there is no cure for AD. The drug therapy used for the AD is only to control the symptoms of the disease but not to reduce the progression of the disease (67). Currently, cholinesterase inhibitors are used as first line drugs for the treatment for AD (3). Cholinesterase inhibitors are approved to treat mild to moderate disease, and weaker evidence shows some effects in severe AD (68). Prior to the approval of rivastigmine and glutamine, the latest treatment guidelines were published and however, both guidelines recommend the use of cholinesterase inhibitors in patients with mild to moderate stages of dementia (69, 70). AD primarily damages glutamate and acetylcholine producing neurons and their associated synapses and this damage correlates well with early cognitive systems of AD (71).

Cholinesterase Inhibitors

In AD patients Cholinesterase inhibitors help to improve memory function and attention by interfering with breakdown of acetylcholine, thereby at synapses increasing the levels of neurotransmitters (72).

• Tacrine: To increase the cholinergic activity researchers began to examine in early 1980’s. Terrine was the first drug to be examined in systemic fashion. The use of terrine has been replaced with more safe and tolerable cholinesterase inhibitors for all practical purposes. The main side effect of terrine was hepatotoxicity.

• Donepezil: Donepezil is a piper dine cholinesterase inhibitors especially for inhibition of acetyl cholinesterase as compared to butylycholinase (73). The reason for donepezil approval was due to both donepezil 5mg and 10mg are efficacious (74-77). The initial dose of donepezil is 5mg / day in morning and titrated to 10mg/ day after 4-6weeks. The side effects of donepezil are few such as nausea, vomiting and diarrhea than with specific cholinesterase inhibitors such as terrine (76). Donepezil potential drug interactions are inadequately evaluated.

• Rivastigmine: Rivastigmine now available as the 3rd cholinesterase inhibitor. Rivastigmine has lower activity at the periphery and has central activity at acetyl cholinesterase and butyl cholinesterase. The approval of rivastigmine indicate that doses of 6-12mg/day are efficacious (79-81). The initial dose of rivastigmine is 1.5mg Bid and titrated upward at a minimum of 2 weeks intervals to a maximum daily dose of 12 mg. Rivastigmine has cholinergic side effects but it was well tolerated in clinical studies (79-81). Rivastigmine has low peripheral side effects (78). Because of the low protein binding, potential drug interactions are low (82).

• Galantamine: It is the 4th approved cholinesterase inhibitor, which has the activity of nicotinic receptor agonist. Galan amine is studied in two randomized placebos - controlled trials (83, 84). The initial dose of glutamine is at 8mg/day with dosage titration of 8mg/day occurring at 4week intervals.

* Donepezil has the longer elimination half-life (70-80hrs) in comparison with other cholinesterase inhibitors (0.3-12hrs) (85).

<table>
<thead>
<tr>
<th>Dose</th>
<th>Tacrine</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
<th>Galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting</td>
<td>mg qid</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
</tr>
<tr>
<td>Maintain</td>
<td>20-40</td>
<td>5-10 mg</td>
<td>3-6 mg</td>
<td>8-16 mg</td>
</tr>
<tr>
<td>TimeBetw</td>
<td>4-8</td>
<td>4-6 mg</td>
<td>2 weeks</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Antioxidants

One study compared the use of vitamin - E 1,000 IU bid, selenide 5mg bid, the combination and placebo in the treatment of moderately impaired AD patients (86). Vitamin- E and selegiline both are superior to placebo. In mildly demented patients, 15months double- blind demonstrated that effect with selegiline 10mg daily there was mild decrease in Brief Psychiatry Rating Scale scores (67).

Estrogen

Estrogen has direct effect in improving the blood flow of deceased vessels in the regions of brain affected by AD. Estrogen has also direct effects on neuronal functions such as, preservation of neurons and repairing the neurons which are damaged by the disease process (88). The majority of the patients with AD manifest non cognitive symptoms at some point of illness (90-91). The symptoms are divided into 3categories: psychic symptoms, inappropriate or disruptive behavior and depression. Treatment strategies for psychiatric or behavioral symptoms include both pharmacological interventions and environmental (antipsychotics, anti-depressants, mood stabilizers, anxiolytics).

Medications used in treating Non-Cognitive Symptoms

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>DOSE</th>
<th>INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>12.5-100 mg</td>
<td>Disruptive behavior:</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5-4 mg</td>
<td>agitation, aggression.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5-10 mg</td>
<td>psychosis,</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5-200 mg</td>
<td>hallucination</td>
</tr>
<tr>
<td>Resperidone</td>
<td>0.2-2 mg</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>10-20 mg</td>
<td>DEPRESSION: poor appetite</td>
</tr>
<tr>
<td>Desipramine</td>
<td>50-150 mg</td>
<td>hopelessness,</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5-20 mg</td>
<td>agitation.</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25-150 mg</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10-40 mg</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>75-400 mg</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-200 mg</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


2. http://www.who.int/news-room/fact-sheets/detail/dementia


17. Alzheimer's Association ; Fact sheet.


19. https://www.ninds.nih.gov/Disorders/All-Disorders/Alzheimers-Disease-Information-Page


27. www.mayoclinic.org > dxc 2016 7103


31. www.google.co.in/search? q=Alzheimer's disease


54. https://www.nice.org.uk/guidance/ng97


88. The role of estrogen in treatment of AD: Stanley J. Brige, MD from the division of Geriatrics , Washington University school of medicine. at Louis, MO


© 2018 by the authors; licensee MJPMS, India. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/)