An Updated Review on Alzheimer's Disease

Tarun Vij*[1], Yash Prashar[1], Dr. Naresh Singh Gill[1], Dipesh Jain[1]

1. Rayat Institute of Pharmacy, Railmajra, SBS Nagar, Punjab, India

Abstract

Preliminary data support the hypothesis that the decline of all higher cognitive functions in senile dementia of the Alzheimer type is attributable to histopathological changes in the hippocampal formation, with or without neocortical neuronal lesions[1]. Alzheimer's disease is the most common form of dementia (non-specific syndrome in which affected areas of brain function may be affected ; such as memory, language). It was first described by German psychiatrist and neuro-pathologist, Alois Alzheimer in 1906 and was named after him. Research indicates that the disease is associated with plagues and tangles in the brain[2].

Key words:- Introduction, sign and symptoms, causes, stages of Alzheimer's, pathophysiology, diagnosis, medication.

Introduction

Alzheimer's disease is an irreversible, progressive brain disorder related to changes of inner nerve cells that result in the death of brain cells[3]. Most often, Alzheimer disease is diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050[4]. Although Alzheimer's disease develops differently for every individual, there are many common symptoms. Early symptoms are often mistakenly thought to be 'age-related' concerns, or manifestations of stress. The disease may cause a person to become confused, lost in familiar places, misplace things or have trouble with language. Research into its symptoms, causes, risk factors and treatment has gained momentum only in the last 30 years. Although research has revealed a great deal about Alzheimer's, the precise changes in the brain that trigger the development of Alzheimer's, and the order in which they occur, largely remain unknown[5]. The only exceptions are certain rare, inherited forms of the disease caused by known genetic mutations.

As of 2012, more than 1,000 clinical trials have been or are being conducted to test various compounds in AD. Mental stimulation, exercise and a balanced diet have been suggested as ways to delay cognitive symptoms (though not brain pathology) in healthy older individuals, but there is no conclusive evidence supporting an effect. Despite the lack of disease-modifying therapies, studies have consistently shown that active medical management of Alzheimer's and other dementias can significantly improve quality of life through all stages of the disease for individuals with dementia and their caregivers[6,7].

Around 0.1% of the cases are familial forms of autosomal (not sex-linked) dominant inheritance, which usually have an onset before age 65. This form of the disease is known as early onset familial Alzheimer's disease. Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilins 1 and 2. Most mutations in the APP and presenilin genes increase the production of a small protein called $A_{\beta}42$, which is the main component of senile plaques[8]. Some of the mutations merely alter the ratio between Aβ42 and the other major forms—e.g., Aβ40—without increasing Aβ42 levels. This suggests that presenilin mutations can cause disease even if they lower the total amount of A_{β} produced and may point to other roles of presenilin or a role for alterations in the function of APP and/or its fragments other than A_{β}. There exist variants of the APP gene which are protective[9].

Active management includes:

(1) appropriate use of available treatment options,

(2) effective management of coexisting conditions

(3) coordination of care among physicians, other health care professionals and lay caregivers.

There are several organizations dedicated to educating patients, families, and caregivers about Alzheimer's, providing helpful insights into where to go for help and support[10].

SIGNS AND SYMPTOMS:-

Although the early signs and symptoms of Alzheimer's disease may vary from person to person, increasing memory loss over time is often the first noticeable symptom.

10 warning signs of Alzheimer's disease are:-

1. **Memory loss that disrupts daily life**: One of the most common signs of Alzheimer's disease, especially in the early stages, is forgetting recently learned information. Others include forgetting important dates or events, asking for the same information over and over and increasingly needing to rely on memory aides (e.g., reminder notes or electronic devices) or family members for things they used to handle on their own.

2. **Challenges in planning or solving problems:** Some people may experience changes in their ability to develop and follow a plan or work with numbers. They may have trouble following a familiar recipe or keeping track of monthly bills. They may have difficulty concentrating and take much longer to do things than they did before.

3. **Difficulty completing familiar tasks at home, at work or at leisure**: People with Alzheimer's disease often find it hard to complete daily tasks. Sometimes, people have trouble driving to a familiar location, managing a budget at work or remembering the rules of a favorite game.

4. **Confusion with time or place:** People with Alzheimer's can lose track of dates, seasons and the passage of time. They may have trouble understanding something if it is not happening immediately. Sometimes they may forget where they are or how they got there.

5. **Trouble understanding visual images and spatial relationships**: For some people, having vision problems is a sign of Alzheimer's disease. They may have difficulty reading, judging distance and determining color or contrast, which may cause problems with driving.

6. **New problems with words in speaking or writing**: People with Alzheimer's may have trouble following or joining a conversation. They may stop in the middle of a conversation and have no idea how to continue or they may repeat themselves. They may struggle with vocabulary, have problems finding the right word or call things by the wrong name (e.g., calling a watch a "hand clock").

7. **Misplacing things and losing the ability to retrace steps**: A person with Alzheimer's disease may put things in unusual places. They may lose things and be unable to go back over their steps to find them again. Sometimes, they may accuse others of stealing. This may occur more frequently over.

8. **Decreased or poor judgment**: People with Alzheimer's may experience changes in judgment or decision making. For example, they may use poor judgment when dealing with money, giving large amounts to telemarketers. They may pay less attention to grooming or keeping themselves clean.

9. **Withdrawal from work or social activities**: A person with Alzheimer's may start to remove themselves from hobbies, social activities, work projects or sports. They may also avoid being social because of the changes they have experienced.

10. **Changes in mood and personality**: The mood and personality of people with Alzheimer's can change. They can become confused, suspicious, depressed, fearful or anxious. They may be easily upset at home, at work, with friends or in places where they are out of their comfort zone[11].

CAUSES:-

A number of causes have been identified as relevant to the onset of Alzheimer's disease.

1. **Plaques and tangles:**

Neuritic plaques and neurofibrillary tangles are present in the AD brain. Scientists, however, do not know if they occur primarily because of the loss or death of neurons or if they occur secondarily as a result of the disease process. Plaques are lesions in the brain that are found outside of the cells, whereas NTs are found within the cells or neurons. NPs consist of a protein called beta-amyloid protein, which is enclosed by a mass of damaged neurons. NTs are inside the neuron and consist of a bundle of abnormally formed proteins called tau proteins. These abnormal formations of tau proteins within the cell disrupt normal cellular function and eventually lead to neuron death.

2. **Inflammation:**

Cytokines are proteins that play a role in both the body's immune system and in inflammation. Inflammation is thought to be another variable in the Alzheimer's process. This is because head injury or other major trauma to the brain is a known associated risk factor for AD. A study by the National Institute on Aging compared World War II veterans with head injury to those who did not. Preliminary information associated head injury with a risk of developing AD. Veterans who had mild head injuries with no skull fractures, and loss of consciousness for less than 30 minutes, had two times the risk of developing AD. Veterans who had head injuries that were more serious, those requiring hospitalization and who were unconscious for greater than 24 hours, had four times the risk of developing AD.

Cytokines are also thought to be neurotropic, which means they may play a part in the growth and development of neurons. Therefore, research into medications to treat AD involves looking at cytokines and the inflammatory process along with their potential neurotropic effect. Other inflammatory factors of particular interest are the cyclooxygenase (COX) enzyme and its products called prostaglandins. Excess amounts of these factors increase levels of glutamate, an amino acid that excites nerves and, when overproduced, is a powerful nerve killer.

3. **Oxidation:**

As beta-amyloid protein breaks down, it releases unstable chemicals called oxygen free radicals. Once released, oxygen free radicals bind to other molecules through a process called oxidation. Oxidation is known to play a role in many serious diseases, including coronary artery disease and cancers, and experts believe it may also contribute to Alzheimer's disease[12].

Causes on the bases on hypoyhesis:-

1. **Cholinergic hypothesis:**

The oldest, on which most currently available drug therapies are based, is the cholinergic hypothesis, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid, leading to generalized neuroinflammation[13].

2. **Amyloid hypothesis:**

In 1991, the amyloid hypothesis postulated that beta-amyloid (A_β) deposits are the fundamental cause of the disease. Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit AD by 40 years of age. Also, a specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD. Whilst apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid buildup in the brain. Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits. In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal connections in the brain in the fast-growth phase of early life may be triggered by ageing-related processes in later life to cause the neuronal withering of Alzheimer's disease. N-APP, a

fragment of APP from the peptide's N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known as TNFRSF21). DR6 is highly expressed in the human brain regions most affected by Alzheimer's, so it is possible that the N-APP/DR6 pathway might be hijacked in the ageing brain to cause damage. In this model, beta-amyloid plays a complementary role, by depressing synaptic function[14,15,16].

3. **Tau hypothesis**:

The tau hypothesis is the idea that tau protein abnormalities initiate the disease cascade. In this model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies[17]. When this occurs, the microtubules disintegrate, collapsing the neuron's transport system. This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells[18].

4. **Other hypotheses**:

Another hypothesis asserts that the disease may be caused by age-related myelin breakdown in the brain. Iron released during myelin breakdown is hypothesised to cause further damage. Homeostatic myelin repair processes contribute to the development of proteinaceous deposits such as beta-amyloid and tau[19].

STAGES OF ALZHEIMER'S DISEASE

Alzheimer's disease generally progresses through three stages: mild, moderate and severe. People experience the three stages at different rates, and there can be an overlap in symptoms from one stage to another.

Stage 1: **Mild Alzheimer's disease**

The mild stage of Alzheimer's disease can last from 2 to 4 years or longer.

Those in this phase of the disease may:

• Say the same thing over and over
• Lose interest in things they once enjoyed
• Have trouble finding names for common items
• Lose things more often than normal
• Seem to experience personality changes
• Have difficulty grasping complex ideas

People with mild Alzheimer's disease are usually alert, sociable, and enjoy life, but their forgetfulness can interfere with daily living and may frustrate them. They may be overly emotional and temperamental.

Stage 2: **Moderate Alzheimer's disease**

The moderate stage of Alzheimer's disease is often the longest, lasting from 2 to 10 years.

In this stage, a person may:

• Get lost easily, even in places they know well
• Become more confused about recent events
• Need assistance with or supervision with tasks such as dressing or washing
• Argue more than usual
• Believe things are real when they are not
• Experience restlessness and agitation
• Have difficulty sleeping and may wander

People with moderate Alzheimer's disease often require close supervision and it may be that services such as day care or home care become necessary.

Stage 3: **Severe Alzheimer's disease**

The severe stage can last from 1 to 3 years or longer. People with severe Alzheimer's Disease cannot do things on their own anymore.

They may not be able to:

• Use or understand words

• Recognize family members
• Care for themselves
• Move around independently
Constant care, 24 hours a day, seven days a week, is usually necessary[20].

Pathophysiology

Neuropathology:
Alzheimer's disease is characterised by loss of neurons and synapsis in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. Degeneration is also present in brainstem nuclei like the locus coeruleus[24]. Studies using MRI and PET have documented reductions in the size of specific brain regions in people with AD as they progressed from mild cognitive impairment to Alzheimer's disease, and in comparison with similar images from healthy older adults.
Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD. Although many older individuals develop some plaques and tangles as a consequence of ageing, the brains of people with AD have a greater number of them in specific brain regions such as the temporal lobe[21] (Fig. 1).

Disease Mechanism
Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ion homeostasis, induces programmed cell death (apoptosis). It is also known that Aβ selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilization of glucose by neurons. Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer's disease[22].

MEDICATIONS
Classification

At the present time, there are only two drug classifications that have been approved in the US by the Food and Drug Administration to treat Alzheimer’s.

1. **Acetylcholinesterase inhibitors:** Tacrine, Rivastigmine, Galantamine and Donepezil
2. **N-methyl-D-aspartate (NMDA) receptor antagonists:** Memantine

Acetylcholinesterase inhibitors

Reduction in the activity of the cholinergic neurons is a well-known feature of Alzheimer's disease. Acetylcholinesterase inhibitors are employed to reduce the rate at which acetylcholine (ACh) is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons. Only donepezil is approved for treatment of advanced AD dementia[23].

The most common side effects are nausea and vomiting, both of which are linked to cholinergic excess. These side effects arise in approximately 10–20% of users and are mild to moderate in severity. Less common secondary effects include muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production[24].

N-methyl-D-aspartate (NMDA) receptor antagonists
Memantine is a noncompetitive NMDA receptor antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate. Memantine has been shown to be moderately efficacious in the treatment of moderate to severe Alzheimer's disease. Its effects in the initial stages of AD are unknown.

Reported adverse events with memantine are infrequent and mild, including hallucinations, confusion, dizziness, headache and fatigue[25].

Marketed drugs

1. Aricept (Donepezil)
2. Reminyl (Galantamine)
3. Exelon (Rivastigmine)
4. Ebixa (Memantine)
5.

Other treatments

Antipsychotic drugs

These are modestly useful in reducing aggression and psychosis in Alzheimer's disease with behavioural problems, but are associated with serious adverse effects, such as cerebrovascular events, movement difficulties or cognitive decline, that do not permit their routine use. When used in the long-term, they have been shown to associate with increased mortality.

Vitamin E

"Doctors sometimes prescribe vitamin E to treat cognitive Alzheimer's symptoms. No one should take vitamin E to treat Alzheimer's disease except under the supervision of a physician". Some studies suggest that taking Vitamin E can slow the progression of Alzheimer's disease. There is some evidence that a diet rich in natural Vitamin E may reduce the risk of developing Alzheimer's disease.

Ginkgo biloba

This is a naturally occurring substance extracted from the Maidenhair tree. It has long been thought to enhance memory. Ginkgo shows some improvement in cognition and social behaviors.

DIAGNOSIS:-

There is no single type of doctor that specializes in diagnosing and treating memory symptoms or Alzheimer's disease. Many people contact their regular primary care physician about their concerns. Primary care doctors often oversee the diagnostic process themselves. There is no single test that proves a person has Alzheimer's. The workup is designed to evaluate overall health and identify any conditions that could affect how well the mind is working.

In many cases, the doctor may refer the patient to a specialist such as a:

- Neurologist who specializes in diseases of the brain and nervous system
- Psychiatrist who specializes in disorders that affect mood or the way the mind works
- Psychologist with special training in testing memory and other mental functions
-

Steps to diagnosis include:-

Understanding the problem

Be prepared for the doctor to ask:

- What kind of symptoms have been occurring
- When they began
- How often they happen
- If they have gotten worse

Reviewing medical history

The doctor will interview the person being tested and others close to him or her to gather information about current and past mental and physical illnesses. It is helpful to bring a list of all the medications the person is taking. The doctor will

also obtain a history of key medical conditions affecting other family members, especially whether they may have or had Alzheimer's disease or related disorders.

Evaluating mood and mental status

Mental status testing evaluates memory, ability to solve simple problems and other thinking skills.
This testing gives an overall sense of whether a person:

- Is aware of symptoms
- Knows the date, time and where he or she is
- Can remember a short list of words, follow instructions and do simple calculations

The doctor may ask the person his or her address. The doctor will also assess mood and sense of well-being to detect depression or other illnesses that can cause memory loss and confusion.

Physical exam and diagnostic tests

A physician will:

- Evaluate diet and nutrition
- Check blood pressure, temperature and pulse
- Listen to the heart and lungs
- Perform other procedures to assess overall health

Blood and urine samples will be collected and other laboratory tests may be ordered. Information from these tests can help identify disorders such as anemia, infection, diabetes, kidney or liver disease, certain vitamin deficiencies, thyroid abnormalities, and problems with the heart, blood vessels or lungs. All of these conditions may cause confused thinking, trouble focusing attention, memory problems or other symptoms similar to dementia.

Other tests include:-

Another recent objective marker of the disease is the analysis of cerebrospinal fluid for beta-amyloid or tau proteins, both total tau protein and phosphorylated tau protein concentrations. Searching for these proteins using a spinal tap can predict the onset of Alzheimer's with a sensitivity of between 94% and 100%. When used in conjunction with existing neuroimaging techniques, doctors can identify people with significant memory loss who are already developing the disease. Spinal fluid tests are commercially available, unlike the latest neuroimaging technology.
Psychological tests for depression are employed, since depression can either be concurrent with AD, an early sign of cognitive impairment, or even the cause.

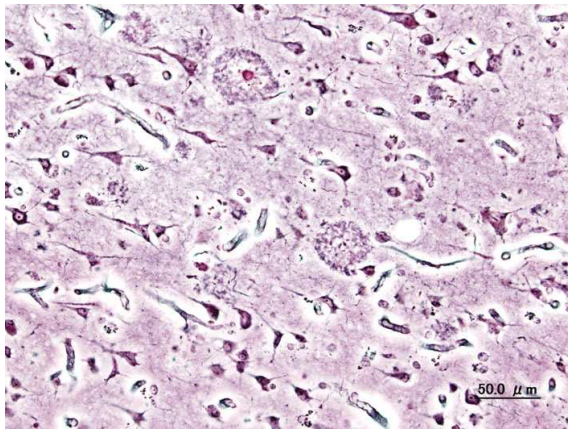
Neurological exam

A doctor, sometimes a neurologist specializing in disorders of the brain and nervous system, will closely evaluate the person for problems that may signal brain disorders other than Alzheimer's.
The physician will also test:

- Reflexes
- Coordination
- Muscle tone and strength
- Eye movement
- Speech
- Sensation

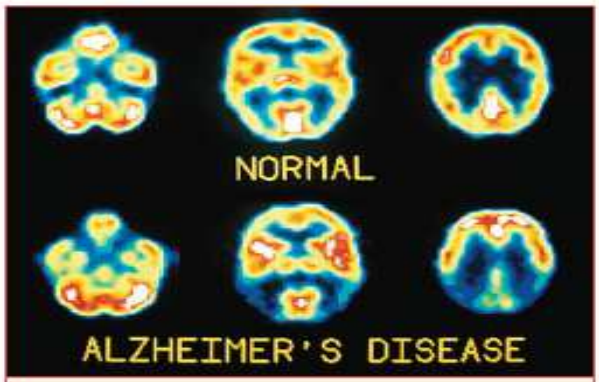
The neurological exam may also include a brain imaging study. The most common types are magnetic resonance imaging (MRI) or computed tomography (CT). MRIs and CTs can reveal tumors, evidence of small or large strokes, damage from severe head trauma or a buildup of fluid. Researchers are studying other imaging techniques so they can better diagnose and track the progress of Alzheimer's. Medicare will cover a positron emission tomography (PET) scan as an aid in diagnosis in certain cases (Fig.2).

(Fig.1)



Histopathologic image of senile plaques seen in the cerebral cortex of a person with Alzheimer's disease of presenile onset.

(FIG.2)



A positron emission tomography (PET) scan showing a normal brain compared with an Alzheimer's brain reveals the severe atrophy that takes place in the Alzheimer's brain. Plaques and tangles are scattered throughout the brain in the last stage (the most severe) of Alzheimer's disease.

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