ALZHEIMERS DISEASE UPON PATHOLOGICAL HYPOTHESIS & THE STAGES OF DISEASE - A REVIEW ON ITS CURRENT AND FUTURE

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Abstract

The pathological hallmark of Alzheimer`s disease is a presence of Amyloid plaques, Neurofibrillary tangles (NFT) and Loss of neuronal connections in brain. Neuronal death is caused due to the aggregation of plaques which causes damage and initiates inflammatory process. The widely accepted pathological hypothesis are amyloid cascade hypothesis, tau hypothesis cascade, mitochondrial hypothesis. The various stages of Alzheimer's disease are normal outward behavior, basic forgetfulness, noticeable memory difficulties, beyond memory loss, decreased independence, severe symptoms, lack of physical control. The mild, moderate and severe forms of Alzheimers were observed during the various condition. Positive lesions due to accumulation and negative lesion due to losses are two different types of neuropathological changes observed in the Alzheimer`s disease. Disease can be diagnosed surely with the findings of autopsy. No evidence-based treatments are available for the Alzheimer's disease. The Alzheimers is managed through Pharmaceutical, Psychosocial and Care giving approach.

Keywords: *Neurodegenerative disorder, Amyloid plaques, Tau, Memantine, Neurofibrillary tangles.*

INTRODUCTION

Alzheimer's is the most prevalent form of Dementia. The functioning of the brain is affected, leading to the disturbance in memory & emotional stability. The diminishing of verbal fluency and impairment of delivering speech is observed. Many environmental & genetic risk factors associated with its development. Alzheimer`s disease attacks nerves cells as well as neurotransmitters. The most common neurodegenerative disorders, most prevalent form of Dementia, in which it does not have any previous causes such as brain trauma or toxicity of alcohol, stroke. Alzheimer's disease is a brain disorder that slowly destroys memory and thinking skills and the ability to carry out the simplest tasks[1].

The Alzheimer's disease was first described in 1907 by Alois Alzheimer. During that time, expectancy of life was less than 50 years. This was most common affecting 10% of the people at the age of 65 and nearly 50% of these aged 85 and women more often than men[2].

The term dementia refers to several illness, which affect the functioning of the brain, leading to the disturbance in memory, emotional stability[3]. Alzheimer's patients, not even recognize their own families also includes reduced verbal fluency and impairment of delivering speech due to failure in the arrangement of words in a proper sequence. There are many environmental & genetic risk factors associated with its development[4].

The disease process is largely associated with amyloid plaques, neurofibrillary tangles and loss of neuronal connections in brain. Alzheimer's disease is currently ranked as the seventh leading cause of death in the United States[5-7].

The Effect of Disease on Economy

Two global studies projected future direct economic cost of Dementia came to be 2trillion dollars by 2030- and 1.6-dollars Trillions by 2050, while a third study projected the direct and indirect cane cost to be 9.12 trillion by 2050.

For Medical Research Support from Government

The Administration on Aging (AOA), within Ach, leads the agency's initiating to support people living with Alzheimer's disease and related dementias and their care givers[8]. The AOA provides funding to states and community-based organizations through the Alzheimer's Disease Programs Initiative (ADPI).

*AOA-Alzheimer's Association of America.

*ADPI-American Dairy Products Institute**.**

DIAGNOSTIC CRITERIA FOR ALZHEIMERS DISEASE

- This disease can be diagnosed surely with the findings of autopsy[9].
- Clinical diagnosis of this disease is "probable" based on their findings.
- Nearly 20% of those chemically diagnosed with Alzheimer's disease may be miss diagnosed[10].
- Alzheimer`s disease is diagnosed based on the persons history from relatives, behavioral observations.
- The absence of alternative conditions supports the diagnosis[11].

- Magnetic Resonance Imaging (MRT) or Computed Tomography (CT) and with single Photon Emission Computed Tomography (SPECT) can be used to help exclude other sub types of dementia[12-15].
- These are 3 steps of criteria for the clinical diagnosis of the spectrum of Alzheimer's disease.
- Definite Alzheimer`s disease is obtained from the biopsy or autopsy[16-19]. In addition to clinical biomarkers, the criteria which is newly proposed includes both the probable and possible Alzheimer`s disease dementia for the use in clinical settings with the evidence of pathophysiological for the research purpose[20].

PATHOPHYSIOLOGY

- Alzheimer`s disease attacks nerves and brain cells as well as neurotransmitters.
- The pathological hallmark of Alzheimer`s disease is a presence of amyloid plaques and neurofibrillary tangles (NFT).
- Presence of plaques and bundles start to destroy connections between the brain cells clumps are known as plaque and bundles[21-24].
- There are two types of neuropathlogical changes in Alzheimer`s disease.
- ❖ Positive lesion due to accumulation.
- ❖ Negative lesion due to losses.
- Pathophysiology of Alzheimer`s not fully known and a lot of research is done to know the pathological process[25-27].
- The widely accepted pathological hypothesis are:
- ❖ Amyloid cascade hypothesis
- ❖ Tau hypothesis cascade
- ❖ Mitochondrial hypothesis.

AMYLOID CASCADE HYPOTHESIS

- According to this hypothesis AB42 amyloid plaques deposition forms in the brain is basic pathology[28].
- AB42 is the secreted by the amyloid precursor protein by the action of β secretase and γ secretase.
- Neuronal death is caused due to the aggregation plaques which causes damage and initiates inflammatory process[29].
- Alzheimer`s occur in two forms
- o Familiar forms
- o Associated with mutation in App gene (chromosome 21), Presenillin -1 (Chromosome 14), Presenillin- 2 (Chromosome 1)

TAU HYPOTHESIS CASCADE

- According to tau hypothesis basic pathology is deposition of tau and formation of neuro fibrillary tangles[30].
- Amyloid deposition occurs secondary to it.
- Tau is a microtubule associated protein which binds and stabilizes the microtubules in intracellular transport[31].

- Hyper phosphorylation of tau alters the tau microtubules therefore it results in microtubules disintegrants leading to reduce axonal transport and cell death.

MITOCHONDRIAL CASCADE HYPOTHESIS

The residual mitochondrial function to handle the free radicals is consider the initializing step in Alzheimer`s disease[32].

STAGES OF ALZHEIMER`S DISEASE

There are seven stages associated with Alzheimer`s disease.

STAGE 1

Normal outward behavior (or) before symptoms appears as,

- It is begin before symptoms are appear it is called "pre-clinical Alzheimer`s disease".
- Likely begin 10-15 years before people have symptoms.
- No treatment for this stage PET scan is the only way to determine whether you or your loved one has Alzheimer`s disease[33-34].

STAGE 2

Basic forgetfulness/very mild changes as,

- You may not notice any big behavioral changes during this stage.
- It is mild early stage we can observe mild forgetfulness in the patient.
- We can also observe problems like loss of concentration[35-36].

In this stage a person still lives independently at this stage, but may have problem like,

- ✓ Remembering a name.
- ✓ Remembering where he or she put an object.
- ✓ Making plan and staying organized.
- May face problem like memory lapses with friend and family.
- These symptoms might not be Alzheimer`s disease at all but simply changes from aging.

STAGE 3

Noticeable memory difficulties as,

- It is a mild decline of memory which is considered as moderate middle stage.
- ✓ Increasing trouble remembering
- ✓ Problems in learning new things
- ✓ Trouble with planning complicated events
- ✓ Trouble remembering their own name, but not details about their own life, such as a dress and phone number
- ✓ Problems with reading, writing and working.
- You will notice changes in reasoning and thinking, asks some question over and over.

STAGE 4

More than memory loss as,

- It is moderate decline.
- Problems in thinking and reasoning.
- ✓ Forget details about themselves having trouble putting right date
- ✓ Forget what month or season it is
- ✓ Trouble in cooking meals
- ✓ Struggle to use telephone
- ✓ Struggle to do multi tasks
- ✓ May lead confusion over the time or place
- Can lead to difficulty with language, organization and calculation.
- This stage can last for many years.
- Increased risk of wondering off or getting lost, changes of sleep pattern such as restlessness at night and sleeping during the day[37-40].

STAGE 5

Decreased independence includes,

- It is moderately severe decline of memory.
- Patient may lose track of where are and what time it is.
- Delusions and hallucinations may also common during this stage.
- Emotional changes are common and paranoia (feeling that others are against you).

STAGE 6

Severe symptoms includes,

- It is a severe decline of memory.
- There are the difficulties in swallow, feed themselves, get dresses. weight-loss, skin infection, pneumonia, trouble walking.
- Communications may also become difficult, increasing in hallucination delusions and paranoia.
- Become moody or with drown or personality changes.
- Restlessness, agitated, anxious or tearful especially in the late night or at late afternoon.

STAGE 7

Lack of physical control includes,

- It is very severe decline of memory.
- These abilities are faded such as eating, sitting, walking, grooming.
- May lose bowel and bladder control.
- May be able to say some words or phrases, but not have a conversation.
- More likely to get infection, especially pneumonia.
- To avoid infections, keep their mouth and teeth clean, treat cuts and scrapes with an antibiotics ointment right away and make sure they get their flu shot every year.

CAUSES OF ALZHEIMER`S DISEASE

Alzheimer`s disease is caused by 3 stages[41-43]

- Mild – early-stage Alzheimer`s disease
- Moderate- middle stage of Alzheimer`s disease
- Severe – late-stage Alzheimer`s disease

Mild Stage

- In early stage forgetting familiar words or the location of everyday objects.
- Symptoms may not be widely possible at that stage.
- Using certain diagnostic rules symptoms can be identified by the doctor.
- At this stage ability of thinking and the memory of the person changes.
- At this stage changes in the personality and also difficulty in expressing thoughts.

Moderate Stage

- Typically it is longest stage can last for many years.
- Symptoms at the stage are known pronounced.
- In middle stage Alzheimer's person may confuse words, get frustrated or angry.
- In the brain the nerves are get damage person get difficult to express though and perform to routine task without benefit (assistance).
- During this stage slowly increasing poor judgement deepening confusion.

Severe Stage

- In this mental function continuous to decline and the disease has a growing impact, movement and physical capabilities.
- At this late-stage Alzheimer's individuals lose the ability to respond to the environment and to control movement.
- Due to this severe stage of Alzheimer's person may say words but communicating path may become difficult.
- At the stage person become unable to walk without any support muscles may become rigid and reflexes abnormal.
- In decline in physical such as person losses the ability to swallow and control bladder and bowl functions.

TREATMENT AND MANAGEMENT

- No disease-modifying treatments are available to cure Alzheimer's disease and due to this Alzheimer's disease has found on interventions to prevent the progression and the onset.
- No evidence is given which supports any particular measure in preventing Alzheimer's.
- Epidemiological studies had purposed relation between an individual likely hood of developing Alzheimer's disease and modifiable factors which includes medications, lifestyle and diet.
- The interventions have some challenges in the determination for Alzheimer's disease, act as primary prevention method and a secondary prevention method[44].

- These challenges include duration of intervention, lack of standardization of inclusion criteria regarding biomarkers specific for Alzheimer's disease.
- Cardiovascular risk factor includes diabetes, hypertension and smoking are associated with a higher risk of onset.
- Use of statins to lower cholesterol may be benefit in Alzheimer's disease.
- Anti-hypertensive & anti-diabetic medications in individuals without overt cognitive impairment may disease of dementia by influencing cerebrovascular pathology.
- With an increased risk for Alzheimer's disease, depression is associated and the sleep disorder.
- By the adequate sleep (approx 7-8 hours) every night, because a potential lifestyle intervention, to prevent in the development of Alzheimer's disease.
- Stress is the risk factor in the development of Alzheimer's strategies to reduce stress and relax the mind may be helpful in preventing the Alzheimer's disease[45-46].

MANAGEMENT

- There's no cure for Alzheimer's disease
- Treatments are divided into three types[47-50]

❖ Pharmaceutical
❖ Psychosocial
❖ Care giving

Pharmaceutical

Medications that are used to treat problems of Alzheimer's disease includes; ACH inhibitors includes Memantine and NMDA receptor antagonists.

- ACH inhibitors are intended for "mild to severeAlzheimer's" and Memantine is intended for "moderate to severe Alzheimer's". The activity of cholinergic neurons reduction is known features of Alzheimer's disease.
- The use of these drugs in mild cognitive impairment did not show any effect in delay of onset of action.
- Common side effects include nausea and vomiting.
- Common secondary effects include bradycardia, increased gastric production.
- An extract of *Ginkgo Biloba,* which is known as EGb 761 has been widely used for the treatment of Alzheimer's.
  - EGb 761 is the only one which showed improvement in the symptoms of both alzehimers and vascular dementia.
  - EGb 761 is neuroprotective, a free radical scavenger, and modulators serotonin and dopamine levels.
- A typical antipsychotics are modestly useful in reducing aggression and psychosis in people with Alzheimer's disease.

Psychosocial

- Psychosocial interventions are used as an adjunct to the pharmaceutical treatment and can be classified within behavior, emotion, cognition or stimulation oriented.

- Attempts to identify and reduce the antecedents and the consequences of problem behaviors.
- Music therapy is effective in the reducing of psychological symptoms.
- Emotion - oriented interventions includes validation therapy sensor integration also called Snoezelen and SPT.
- SPT stimulated presence therapy is based on attachment theories and this involves in playing a recording of the closest relative voices of the person with Alzheimer's disease.
- Cognitive retraining tries to improve impaired capacities by exercising mental abilities.
- Stimulation-oriented treatment includes music, art, pet, exercise, other kind of recreational activities.
- Stimulations has the modest support for improving the behavior, mood, function.

Care Giving

- People are incapable of trending to their own needs.
- Essential treatment.
- Carefully managed over the course of the disease.
- During the final stages of the disease, treatment is centered on receiving the discomfort until death, often with the ***hospice***.

SUMMARY & CONCLUSIONS

Most common type of dementia, it is a progressive disease beginning with a mild memory loss and possibly leading to loss of ability to carry on a conversation and respond to the environment. This disease involves parts of the brain that controls thoughts, memory and language. Main causes are abnormal build up protein in and around brain cells. One of the proteins involved is called "**Amyloid**" deposits of which from plaques around brain cells. The other protein called **Tau** deposits of which forms tangles within brain cells.

Dementia is a degenerative disease that affect a person`s ability to live independently. In the 3 main types of dementia Alzheimer's disease is common type of disease is delirium and dementia. Although people with dementia often exhibit behaviors that are challenging for family and professional care givers to manage the behaviors are caused by damage to the brain and are not interventional. There will be further a long challenge is communication. The caregivers may be able to determine the underlying need and learn how to alleviate the challenging behavior. People with dementia need to be treated with kindness activities of daily living are disrupted in those with dementia, as the dementia get worse family members and care givers must step in an assist with personal care and household can provide a sense accomplishment and well-being. Education and training in ethical decision making and conflict resolution are invaluable tools to improve the experiences of those dementia.

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