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4. ALZHEIMER'S DISEASE

PREPARED BY

DR. NAITIK D. TRIVEDI,

M. PHARM, PH. D

LECTURER AT GOVERNMENT AIDED,

A. R. COLLEGE OF PHARMACY & G. H. PATEL INSTITUTE OF PHARMACY, VALLABH VIDYANAGAR, ANAND, GUJARAT

Mobile: +91 - 9924567864

E-mail: mastermindnaitik@gmail.com

&

DR. UPAMA N. TRIVEDI,

M. PHARM, PH. D

ASSOCIATE PROFESSOR & HoD (Pharm.D),

INDUBHAI PATEL COLLEGE OF PHARMACY AND RESEARCH CENTRE, DHARMAJ, GUJARAT

E-mail: ups.aasthu@gmail.com

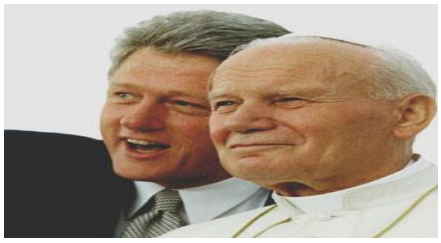
ALZHEIMER'S DISEASE

INTRODUCTION:

- A condition characterized by a specific group of signs and symptoms
- Alzheimer's Disease is the most common form of Dementia.
- Brain disorder that affects the ability to control thought, memory, and language
- Symptoms are different for each individual.

CAUSES:

- No known single cause
- Involves the malfunction or death of nerve cells
- Strokes increase risk
- Brain damage occurs years before first symptoms appear
- Nerve cells that process, store, and retrieve information have already begun to die when symptoms emerge



Pope John Paul II

TEN WARNING SIGNS:

1. Memory loss
    - Forgetting recently learned information
    - Most common early stage sign
2. Difficulty performing familiar tasks
    - Failure preparing a meal, placing a telephone call or playing a game
    - Hard to plan or complete everyday tasks
3. Problems with language
    - Forget simple words
    - Substitute words ("that thing for my mouth" instead of "toothbrush")
4. Disorientation to time and place
    - Become lost in own neighborhood
    - Forget where they are and how they got there
    - Not know how to get back home
5. Poor or decreased judgment
    - Inappropriate dress (layers on a warm day or little clothing in cold)
    - Poor judgment (give away large sums of money to telemarketers)
6. Problems with abstract thinking
    - Difficulty performing mental tasks (using numbers)
7. Misplacing things

- Put things in unusual places (iron in freezer, wristwatch in sugar bowl)

8. Changes in mood or behavior
    - Rapid mood swings (calm to tears to anger for no apparent reason)
9. Changes in personality
    - Personality changes dramatically
    - Extremely confused, suspicious, fearful or dependent on family
    - Anxiety, agitation, and delusions or hallucinations are seen
10. Loss of initiative
    - May become very passive (sitting in front of the TV for hours, sleeping more than usual, not wanting to do usual activities)

STAGES:

Alzheimer's can be broken up into three stages:

- **Early**
- **Middle**
- **Late**

Early Stage:

*Can last from virtually no time to about five years.

Characteristics:

- Difficulty remembering most recent information
- Difficulty performing familiar tasks
- Decreased or altered judgment
- Language Changes
- Changes in personality, behavior, & mood
- Disoriented with time and place
- Problems with abstract thinking

Middle Stage:

*Lasts anywhere from 2 and 12 years

*Symptoms are usually more obvious in this stage.

Characteristics:

- Remembers less and less (Forgets quicker than in Early Stage)
- Increased difficulty or inability to perform familiar tasks

- Lack of judgment
- Increased changes in behavior, mood, and personality (suspiciousness)
- More confused about time and place
- Loss of ability to think abstractly
- Changes in the five senses
- Changes occur physically (loss of bladder control, less steady while walking, etc.)

Late Stage:

*Lasts about 1 to 3 years

Former US President Ronald Reagan

Characteristics:

- Little or no short term memory remains
- Unable to perform tasks
- Lack of judgment
- Unable to communicate effectively
- Doesn't recognize self or family
- Puts things in their mouth or touches & grabs things
- Five senses have little or no function
- Physical activity declines (loss of ability to walk and/or trouble swallowing)

PATHOPHYSIOLOGY:

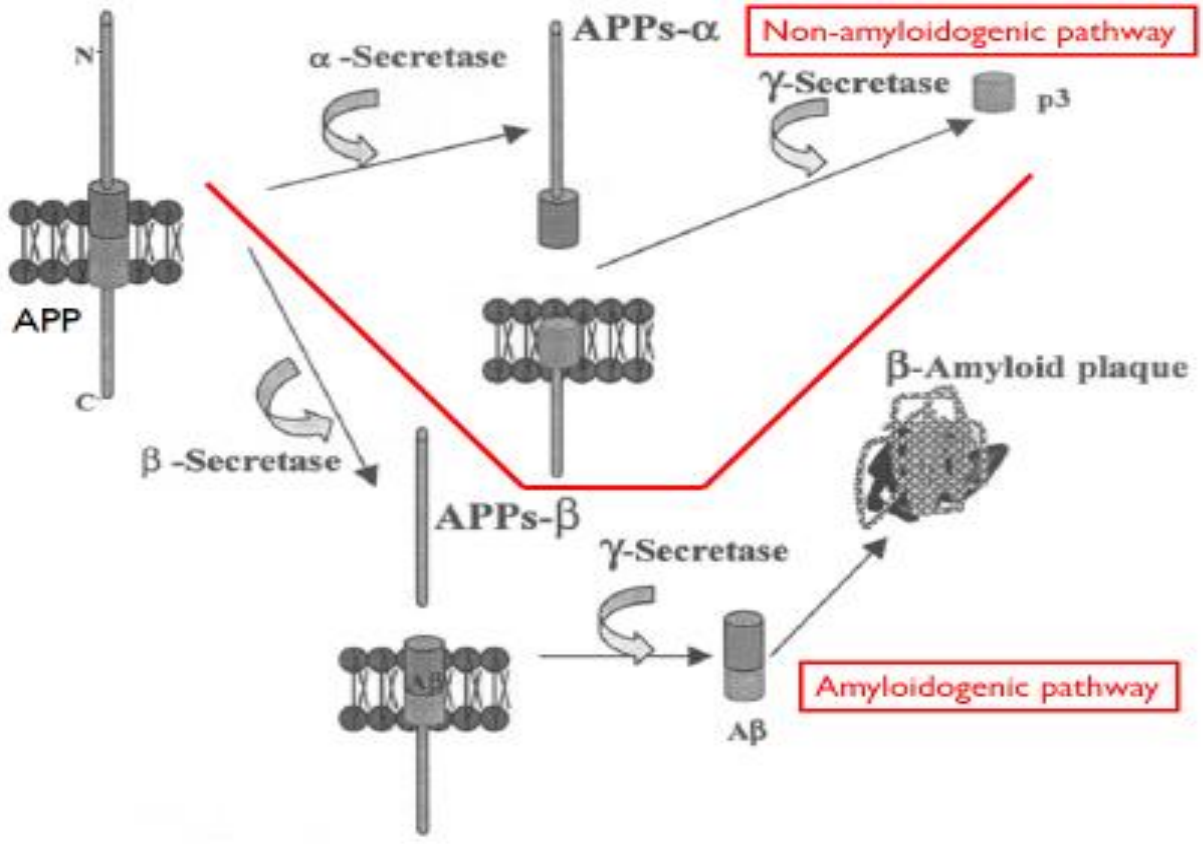
Pathophysiology of Alzheimer's very well described by the below mentioned hypothesis:

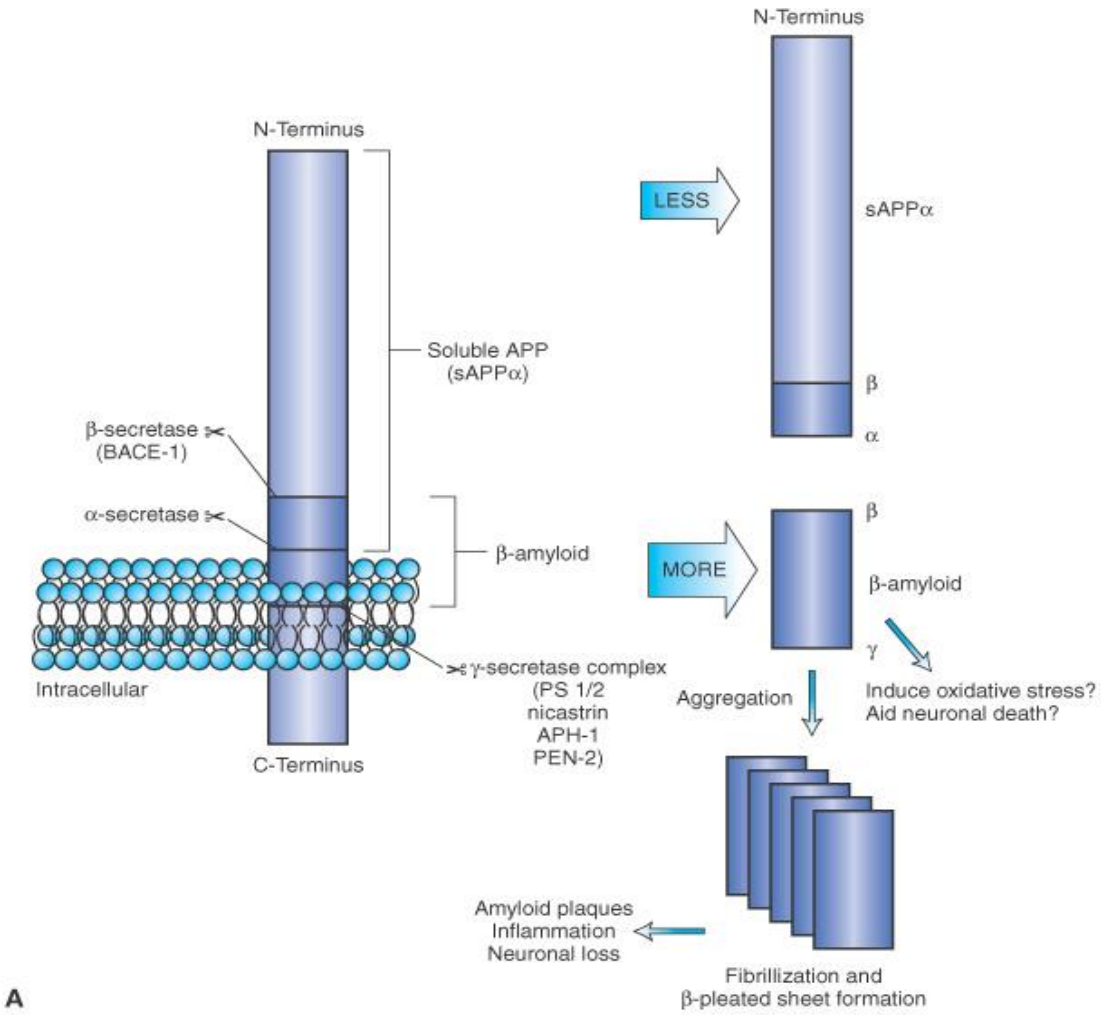
1. β – amyloid plaque hypothesis
2. Neurofibrillary tangles (tau) hypothesis
3. Cholinergic hypothesis
4. Glutamatergic/excitotoxicity hypothesis
5. Oxidative stress hypothesis
6. Chronic inflammation hypothesis
7. Cholesterol hypothesis

Before reading see below video for easy understandin:

1. https://www.youtube.com/watch?v=v5gdH_Hydes&t=4s
2. https://www.youtube.com/watch?v=NjgBnx1jVIU

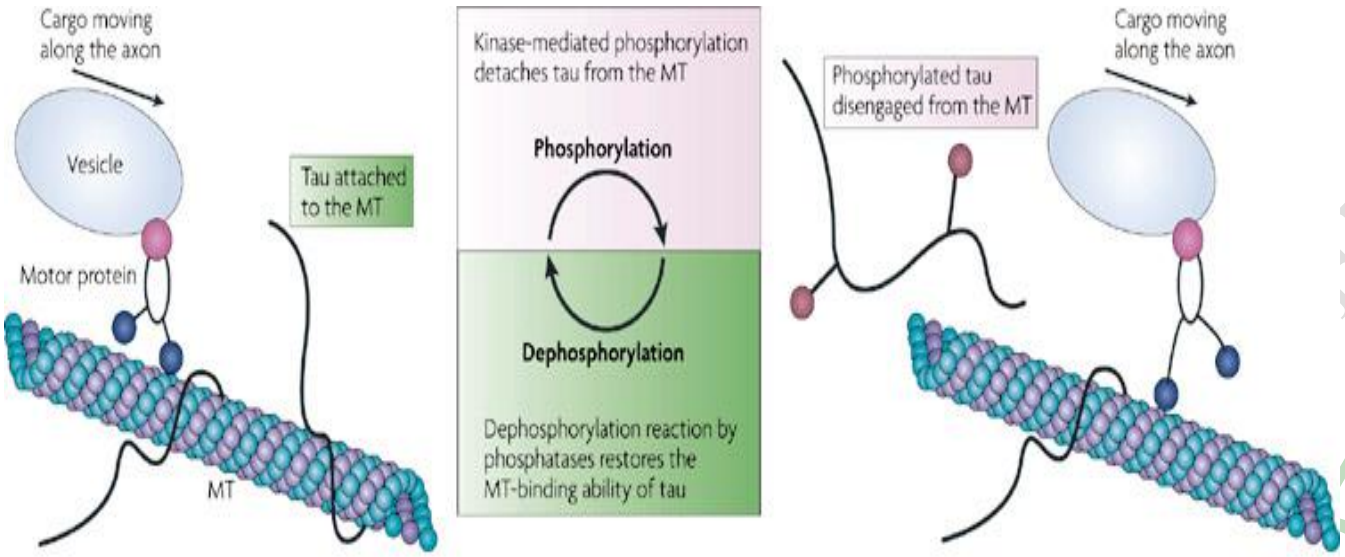
1. **β – amyloid plaque**
   - Amyloid precursor protein (APP) is an integral membrane protein expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been implicated as a regulator of synapse formation, neural plasticity and iron export.
   - Amyloid precursor protein (APP) proteolysis is the crucial step in the development of AD.
   - APP is mainly cleaved by 3 enzymes: α –secretase, β – secretase and γ – secretase.
   - Cleaved by α –secretase followed by γ – secretase produce soluble amino acid (40 amino acid peptides known as Aβ – 40)
   - But cleaved by β – secretase followed by γ – secretase produce insoluble amino acid (42 amino acid peptides known as Aβ – 42) which aggregate and produce clumps known as β – amyloid plaque.

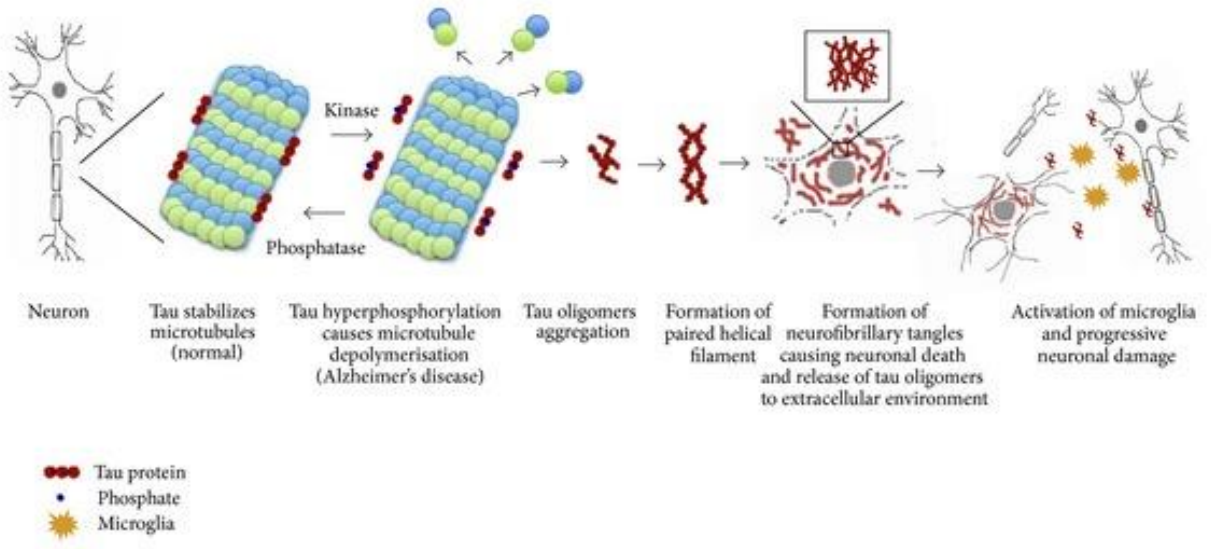




2. Neurofibrillary tangles (tau) hypothesis :

- Neuronal microtubules are essential components of the neuronal cell structures.
- It is useful for the neuronal transmission propagation as well as serve as track for nutrients transportation.
- Tau is the protein attached on the surface of microtubules and it make the bonding between these microtubules.
- In, Alzheimer's Tau protein get hyperphosphorylation due to plaque formation, this process disturb the bonding between microtubules and Tau protein detached from the microtubules surface and produce tangles. So microtubules get collapse and it destroy the neuron's transport and communication system.
- This effect is known as neurofibrillary tangles and it play a main role in alzheimer's disease.





3. **Cholinergic hypothesis**:
   - Loss of cholinergic neurons also play a main role in the formation of alzheimer's disease.
   - Acetylcholine is an important neurotransmitter in brain region involving memory.
   - Loss of cholinergic activities correlated with some aspect of cognitive impairments.
   - Acetylcholine mainly binds on two receptors muscarinic and nicotinic. Nicotinic receptors activation is mainly related with the memory and mood activity.
   - In, alzheimer's patient it is found that loss of 70 % of nicotinic receptors.

4. **Glutamatergic/excitotoxicity hypothesis:**
    - Glutamate is the primarily excitatory neurotransmitter in the brain. Glutamate have a variety of receptors. Out of that N – methyl D –aspartate (NMDA) receptor play a main role in alzheimer's disease.
    - Continuous activation of glutamenergic NMDA receptors leads to chronic calcium influx and it generate excitotoxicity. It also leads to generate APP plaque and hyperphosphorylation in Tau protein.
    - Generally Glutamate is reuptake by the neuronal synapse. But in AD or dementia like condition this process get affected.
5. Oxidative stress hypothesis:
    - In alzheimer's patients Aβ – 42 induced lipidperoxidation produce reactive oxygen and nitrogen species. These nitrogen and oxygen species contain an unpaired extra electrons that react with other molecules to achieve a stable configuration.
    - During this process reactive species form molecular bond with other molecules that time higher energy electron (free electron) thrown off.
    - The reaction is permanent reactive species alter the molecules structurally and functionally where it attached. The free radical left to cause cellular and molecular damage.
    - Brain is highly vulnerable towards the oxidative stress damage because of its high oxygen consumption and low level of antioxidant enzymes.
6. Chronic inflammation hypothesis:
    - β – amyloid deposition, NFTs and damaged neurons stimulate the inflammatory response.
    - So microglia get activate into the brain and release various cytokines and complimentary proteins as well as this effect release the prostaglandins and cyclooxygenase which are the mediators of inflammations that cause the cellular damage of the brain.
7. Cholesterol hypothesis:
    - The brain contains highest amount of the cholesterol than other organs.
    - Study suggest that elevated cholesterol level increase the Aβ production where reduced cholesterol level decrease the Aβ production. Reduced cholesterol level also decrease the risk of dementia.

DIAGNOSIS:

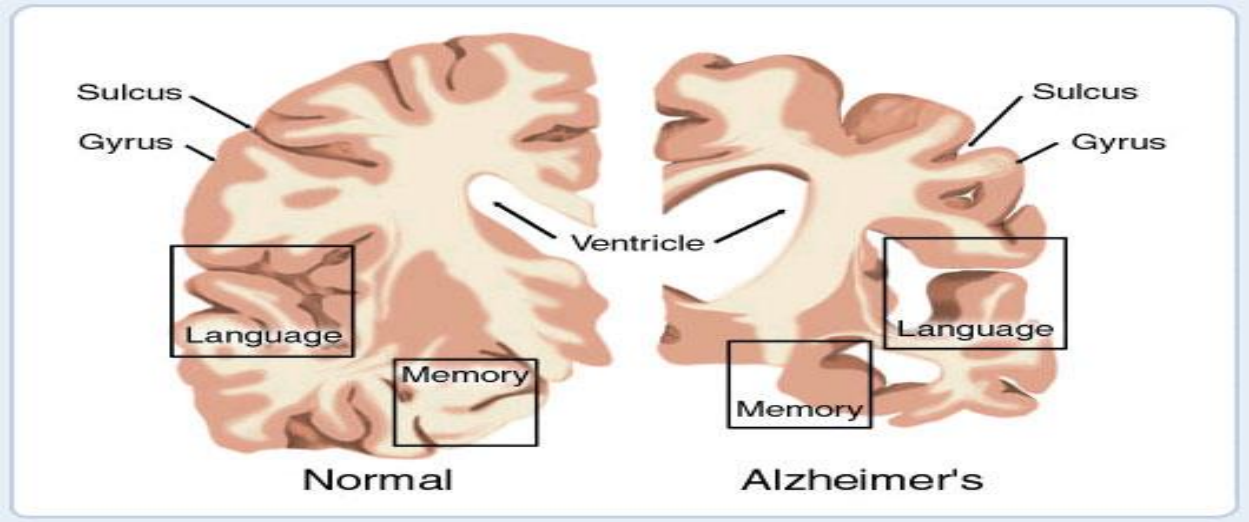
Only definite way to diagnose AD is to do an autopsy of the brain (impossible before death).

No specific test can detect Alzheimer's

- Diagnosis involves multiple tests
- 90% accurate

Tests included:

- Physical examination: nutritional status, blood pressure, and pulse
- Test sensation, balance, and other functions of the nervous system
- Brain scan: detects other causes of dementia such as stroke
- Mental status evaluation assessing:
  - sense of time and place
  - ability to remember, understand, and communicate
  - ability to do simple math problems
- Lab tests: blood & urine (determine other causes of dementia)



Risk Factors:

Increasing age (Greatest known factor)

- Risk doubles every five years after age 65
- Risk is nearly 50 % after age 85

Family history/ Genetics

- A gene has been identified that increases the risk of Alzheimer's
- Not guarantee an individual will develop the disorder
- Found in only a few hundred extended families worldwide

PREVENTION:

- Decrease head injuries
- Keep overall good health of your brain
  - ✓ eat a healthy diet
  - ✓ stay socially active
  - ✓ avoid tobacco, excess alcohol, and other drugs
  - ✓ exercise the body & mind
- Monitor heart and blood vessels conditions which increase risk: heart disease, diabetes, stroke, high blood pressure, & cholesterol

TREATMENTS:

Currently, there is <u>no cure</u>.

- Drug and non-drug treatments may help with cognitive (brain) and behavioral symptoms.
- Drug Treatment:
  - Prevents the breakdown of acetylcholine (a chemical messenger in the brain important for memory and other thinking skills)
  - Keeps levels of acetylcholine high, even while the cells that produce it continue to become damaged or die
  - The first Alzheimer medications to be approved were cholinesterase inhibitors.
  - Memantine and Vitamin E supplements are also used