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A Short Review on Alzheimer's Diseases

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ABSTRACT

Alzheimer's disease acknowledged as progressive neurodegenerative disorder, is the most common type of dementia in aging adults. Pathologically it is characterized by intracellular neurofibrillary tangles and extracellular amyloidal protein deposits contributing to senile plaques. Tremendous progress has been made in understanding the processes of the Alzheimer's disease (AD) cascade, laying the groundwork for improvements in diagnosis and treatment. Understanding cerebral degeneration and accumulation of beta-amyloid has generated hopes for discovery of disease-modifying treatments. Progress is needed in understanding the mechanisms that link beta-amyloid accumulation and neuronal death. Currently available treatments i.e. acetyl cholinesterase inhibitors and NMDA receptor antagonist contribute minimal impact on the disease and target late aspects of the disease. These drugs reduce the progression of the disease, provide symptomatic relief but fail to achieve a definite cure. The purpose of this review is to provide brief introduction to AD, different aspects of pathophysiological mechanisms behind Alzheimer's disease and its management through conventional drug therapy.

INTRODUCTION

Alzheimer's disease is first characterized by Alois Alzheimer in 1907.AD is the most common cause of dementia in the elderly. The disease usually becomesclinically apparent as insidious impairment of higher intellectual function, with alterations in mood and behavior. Later, progressive disorientation, memory loss, and aphasia indicate severe cortical dysfunction, and over the next 5-10 years. The patient becomes profoundly disabled, mute, and immobile. Death usually occurs from inter current pneumonia or other infections. Thepatient has difficulty in dressing and other activities of daily living. They tend to get lost in their own environment. Forgetfulness is the major initial symptom(1).

- Alzheimer's disease is progressive dementia affecting both cognition and behavior with no known cause or cure. Patients eventually lose all cognitive, analytical, physical functioning and the disease is ultimately fatal.
- Alzheimer's disease is a neurological disorder (2).

PATHOPHYSIOLOGY (3):

AD is characterized by progressive loss of brain tissue,extracellular plaques of β- amyloid protein, intracellular neurofibrillary tangles and neuronal degeneration.

Changes in brain structure:	Brain atrophy and neuronal loss occurs starting with the cortex and hippocampus, ultimately progressing throughout the brain.
β- amyloid protein:	Characterized by 3 neuropathologic states: plaques of β-amyloid plaques, NFTs, and neuronal degeneration occur in specific locations in the brain.
	The β- amyloid theory maintains that formation of β-amyloid plaques as the first step and NFTs occur after plaques formation.

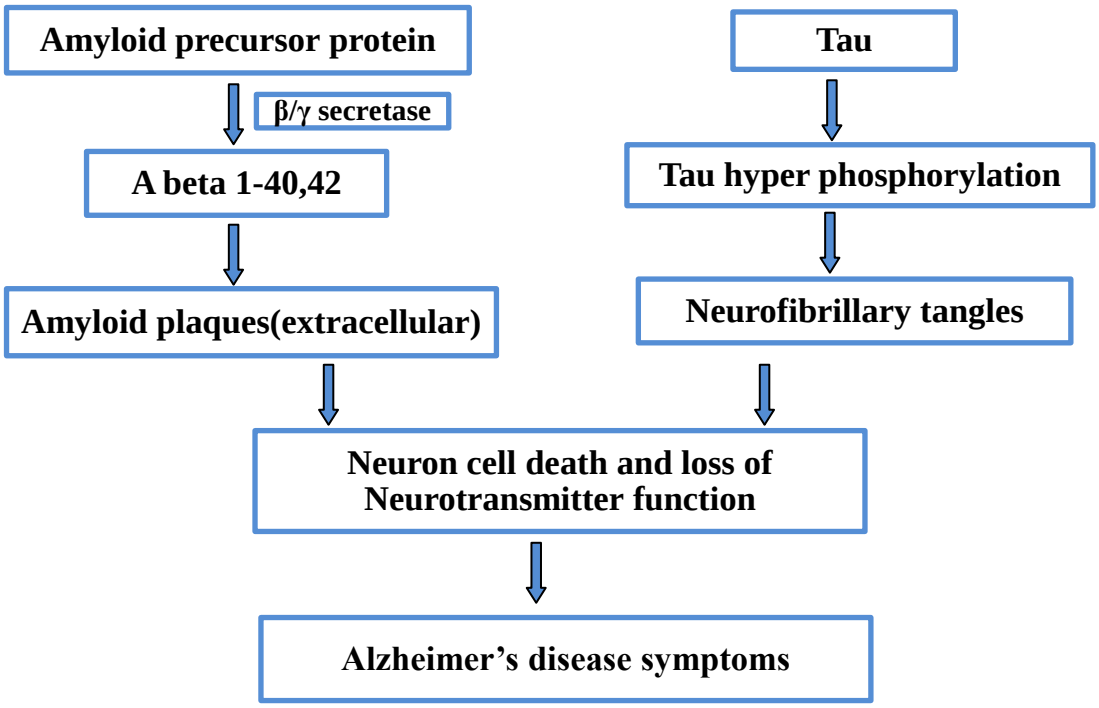

Fig-1: Pathophysiology of Alzheimer's disease

Cholinergic neurons:	Drastic loss of cholinergic neurons.
Glutamate:	Slow and steady activation of a glutamate receptor leads to cellular damage.
Oxidative stress:	β-amyloid induces oxidative stress causing permanent damage to some neuronal macromolecules (especially lipids) and creating reactive species, which further propagate neuronal toxicity.
Chronic inflammation:	The chronic inflammation observed with AD is thought to be the result of all of these mechanisms causing cell damage and death. In AD, inflammatory cytokines respond to these processes and contribute to neuronal destruction because they appear to act uninhibited.
Neurotransmitter deficiency:	Serotonin is an important factor in depression and anxiety, both of which are common in patients with AD.

STAGES OF ALZHEIMER'S DISEASE(4):

Based on MMSE (Mini Mental Status Examination) score

Mild: Patient has difficulty remembering recent events.
Decline in ability to manage finances, prepare food, and carrying out other household activities.

Moderate: Patient requires assistance with activities of daily living.
Frequent disorientation with regard to time (date, year, season).
Severe impairment in recalling of recent events.
Loses ability to drive safely.
Agitation, paranoia and delusions are common.

Severe: Patient loses ability to speak, walk, and feed self.
Incontinent of urine and feces.
Requires care 24 hours a day, 7 days a week.

CLINICAL PRESENTATION (4):

a) Signs:

➔ The patient may have vague memory complains initially or the patients significantother may report that the patient is "forgetfull".

➔ Cognitive decline is gradual over the course of illness. Behavioral disturbances may be present in moderate stages.

➔ Loss of daily function is common in advanced stages.

b) Symptoms:

Cognitive	➢ Memory loss(poor recall and losing items), ➢ Aphasia (circumlocution and Anomia), ➢ Agnosia, ➢ Aproxia, ➢ Impaired executive function and disorientation (impaired perception of time).
Non-cognitive	➢ Depression, psychotic symptoms (hallucination & delusions) behavioral disturbances (physical and verbal aggression), motor hyperactivity. ➢ Uncooperativeness,wandering, repetitive mannerisms & combativeness.
Functional	➢ Inability to care for self (dressing, bathing, eating).

DIAGNOSIS(5,6):

Alzheimer's disease can only be definitely diagnosed by an autopsy of the brain.Researchers are making progress studying biomarkers, brain imaging, and other new techniques.

There is no test that confirms a diagnosis of Alzheimer's. Doctors use a variety of tests to make a probable diagnosis of Alzheimer's disease.

a) Medical History and Physical Examination:

Patient's health history, including other medical conditions the patient has, recent or past illnesses, and progressive changes in mental function, behavior, or daily activities.

Usage of prescription drugs and lifestyle factors including diet and alcohol.

Evaluation of patient's hearing and vision and check blood pressure and other physical signs. A neurological test viz. checking reflexes, coordination, and eye movement.

b) Laboratory Tests:

Evaluation of other possible causes of dementia such as thyroid imbalances or vitamin deficiencies.

Measuring levels of amyloid beta and tau proteins in spinal fluid samples to help identify patients with memory problems who may be at risk for developing Alzheimer's.

c) Neuropsychological Tests:

Psychological tests like assessing difficulties in attention, perception, memory, language, problem-solving, social, and language skills are used.

Commonly used test is the Mini-Mental State Exam (MMSE), which uses a series of questions and tasks to evaluate cognitive function.

d) Brain-Imaging Scans

Imaging tests are useful for ruling out blood clots, tumors, or other structural abnormalities in the brain that may be causing signs of dementia.

- Magnetic resonance imaging (MRI),

- ❖ Computed tomography (CT) or
- ❖ Positron-emission testing (PET) scans.

Assessment for AD(7):

(i) ***Initial exam***(signs to look for): Poor orientation, increased forgetfulness, change in personality and emotional status. Avoidance of typical activities and hobbies, social isolation.
(ii) ***Mental status screening***: Mini mental state, clock drawing, mattis dementia screening, montreal cognitive assessment, clinical dementia rating scale, Geriatric depression scale.
(iii) ***Interview for instrumental activities of daily living***: Medication use, cooking, driving, financial management
(iv) ***Interview for general activities of daily living***: Bathing, Dressing, Toileting
(v) ***Assessment of visual motor skills***(signs to look for): Ideomotor apraxia (skilled movement to verbal command or initiation), ideational apraxia (performing a planned series of tasks to achieve a goal), extra pyramidal motor signs, constructional apraxia, spatial concept- ualization errors
(vi) ***Neuroimaging*****:** Computed tomography (CT), Single photon emission computed tomography(SPECT), Magnetic resonance imaging (MRI), Positron-emission testing (PET)
(vii)***Neuropsychological testing*** (skill areas to assess): Estimate of pre morbid IQ, attention, processing speed, executive functioning, planning, organization, mental flexibility, memory, working memory, long term memory, language, naming, semantic fluency, evidence of perseverations.

TREATMENT (4,5,6):

The goals in treating Alzheimer disease are to

- Slow progression of the disease
- Manage behaviour problems, confusion, and agitation
- Provide a safe living environment
- Support family members and other caregivers

There is no cure for Alzheimer disease. The most promising treatments include lifestyle changes and medications.

a) Non-pharmacological therapy:

- On initial diagnosis, the patient andcaregiver should be educated on the course of illness, available treatments, legal decisions, changes in life style that will be necessarywithdisease progression, other quality of life issues**.**

b) Lifestyle:

Studies show the following lifestyle changes may help improve behaviour in people with Alzheimer disease:

- A regular walk may improve communication skills and reduce the chance of wandering.
- Bright light therapy may reduce insomnia and wandering.
- Calming music may reduce wandering and restlessness, boost brain chemicals, and improve behavior.
- Pets can sometimes help people improve behavior.
- Relaxation training and other exercises that require focused attention may help boost social interaction and make it easier to do tasks.

c) Pharmacotherapy of cognitive symptoms:

- Currentpharmacotherapeutic interventions are primarilysymptomatic attempts to improve or maintain cognition. There is evidence that some interventions (eg: cholinesterase inhibitors, vitamin-E) may prolong the time to critical functional end points.
- They are presently no medications that change the course of illness (or) cure AD.
- Cholinesterase inhibitors: increase the amount of acetylcholine in the brain.

- Ex:Rivastigmine, galantamine, donepezil.

- N-methyl-D-aspartate (NDMA) receptor antagonist:

  - Ex: Memantine

  - Used for treatment of moderate-to-severe Alzheimer's disease. By blocking NDMA receptors, memantine protects against the overstimulation of glutamate, an amino acid that excites nerves and, in excess, is a powerful nerve-cell killer.

d) Pharmacotherapy of noncognitive symptoms:

- *Depression:*Antidepressants like selective serotonin reuptake inhibitors (SSRIs), including fluoxetine and sertraline may help reduce depression, irritability, and restlessness associated with Alzheimer's in some patients.

- *Apathy:* Depression is often confused with apathy. An apathetic patient lacks emotions, motivation, interest, and enthusiasm while a depressed patient is generally very sad, tearful, and hopeless. Apathy may respond to stimulants, such as methylphenidate.

- *Psychosis.* Antipsychotic drugs are used to treat verbally or physically aggressive behaviour and hallucinations. Newer atypical antipsychotics such as risperidone, olanzapine.

- Anti-seizure drugs such as carbamazepineor valproate can also sometimes treat agitation and other psychotic symptoms.

- *Disturbed Sleep.* Patients with Alzheimer's disease commonly experience disturbances in their sleep/wake cycles. Moderately short-acting sleeping drugs, such as temazepam, zolpidem or zaleplon or sedating antidepressants such as trazodone may be useful in managing insomnia.

FUTURE PROSPECTS IN AD(8)

Neurotrophic factors:

Therapeutic strategy for AD is to use multimodel drug that effectively target brain insulin/IGF signaling cascade and also enhances IGF level or other neurotrophic factors, alternatively a mixture of different neurotrophic factors could be useful to attenuate pathogenesis of AD. Cerebrolysin, a mixture of several neurotrophic factors has multi model action on brain cells including neuroprotection, neurodegeneration and angiogenesis, a hope for this drug as potential future drug.

Nanotechnology for treatment:

There is advancement in nanotechnology for diagnostics and drug delivery purposes this is quite likely that therapeutic agents if delivered through nanotechnology will induce long term neuroprotection engineered nanoparticles having high specificity for brain capillary endothelial cell is another way hence further studies are needed.

But unfortunately most of these drugs have side effects like gasto intestinal bleeding, liver and renal toxicity and nausea. These drugs do not work with patients who carry ApoE gene. In this respect natural herbal alternative with pleiotropic useful properties and with least adverse effects provide greater therapeutic benefit than single ingredient synthetic pharmaceutical drug having serious side effects. The complex pathology of AD and heterogenouspharmacological effects of herbal extracts pose difficult challenges in using herbal drugs in AD.

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