EXP NO: **DATE:**

ALZHEIMER'S DISEASE

DEFINITION

Alzheimer's disease(AD) is a progressive dementia with loss of neurons and characterized by the presence of two main microscopic neuropathologic hallmarks NFT (Neurofibrillary tangles) and Amyloid plaques (Senile or neuritic plaques).

EPIDEMOLOGY

- AD accounts for over 60% of cases of late-life cognitive dysfunction.
- The prevalence of AD increases exponentially with age, affecting approximately 7% of individuals aged 65 to 74 years, 53% aged 75 to 84, and 40% of persons aged 85 years and older.
- Approximately 1,00,000 individuals with AD die every year. AD is the eighth leading cause of death in US.

ETIOLOGY

- **Genetics:** Genetic factors have been linked to both early and late onset AD. Alterations to chromosome 1, 14 and 21 have been associated with early onset AD, whereas the presence of apo E4 alleles increase a person's risk of developing late onset AD.
- **Environmental and other factors:** It includes stroke, alcohol abuse, small head circumference, repeated or severe head trauma, Down syndrome and lower levels of education.

PATHOPHYSIOLOGY

➢ NEUROFIBRILLARY TANGLES AND NEURITIC PLAQUES

The brains of AD patients have a drastically increased number of neurofibrillary tangles(NFTs) and neuritic plaques(NPs) in comparison to normal brains. These lesions occur particularly in the hippocampus, amygdale, and cerebral cortex in areas where cholinergic and other brain neuronal pathways have been destroyed.

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NFTs are intracellular and are comprised of paired neurofilaments with a helical shape that aggregate in dense bundles. The paired helical filaments are comprised of an abnormally phosphorylated form of tau protein. Affected cells function improperly and eventually die.

NPs are extracellular and are comprised of a core of beta amyloid protein(beta AP) surrounded by a snarled mass of broken neuritis. Plaque formation seems to precede accumulation of NFTs. The number of NPs parallels disease severity.

- **BETA AMYLOID PROTEIN**

BetaAP deposition may initiate the process of plaque formation. Proteases cleave the amyloid precursor protein(APP)to form the betaAP. Genetic abnormalities of the APP gene on chromosome 21 can lead to overproduction of betaAP. Other early onset cases may be attributed to an Alzheimer's gene located on chromosome 14 that may play a role in the production and cleavage of APP.

- **APOLIPOPROTEIN E**

A subtype of apolipoprotein E (apo E) is a genetic marker for late-onset AD. The gene responsible for the production of apo E is located on chromosome 19. 90% of persons inheriting two copies of apo E4 develop AD BY AGE 80 years, and the onset of symptoms is relatively earlier. Apo E_2 appears to be protective, conferring a relative resistance to AD.

- **INFLAMMATORY MEDIATORS**

Inflammatory mediators and other immune system constituents are present near areas of plaque formation, suggesting that the immune system plays a role in pathogenesis of AD. This could foster disease progression.

- **NEUROTRANSMITTER ABNORMALITIES**

The neuronal pathways most profoundly damaged are the cholinergic pathways. Logically, much research has focused on augmentation of cholinergic transmission at remaining synapses.

Serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are lost, whereas monoamine oxidase type-B (MAO-B) activity is increased. MAO-B is responsible for metabolizing norepinephrine, serotonin, and dopamine. Glutamate and other excitatory amino acid neurotransmitters have been implicated as potential neurotoxin in AD.

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- **EXOGENOUS FACTORS**

Evidence is building suggesting a role for estrogen in the prevention of AD. Repeated or severe head trauma has also been implicated as predisposing to AD. Preliminary in vitro evidence suggests that zinc may accelerate plaque formation from soluble betaAP. Although the use of zinc supplements should be discouraged in patients with AD, at this time zinc should not be considered a cause of the disease.

CLINICAL PRESENTATION

- **Cognitive deficits:**

- Memory loss, poor recall
- Dysphasia
- Dyspraxia
- Disorientation; impaired perception of time; poor sense of direction; cannot recognize acquaintances, family, or self
- Impaired calculation
- Impaired judgement and problem-solving skills.
- Depression

- **Noncognitive Psychiatric symptoms and disruptive behaviors**

Psychotic symptoms:

- Hallucinations
- Delusions
- Suspiciousness

Nonpsychotic disruptive behaviors

- Physical and verbal aggression
- Motoric hyperactivity
- Uncooperativeness

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- Repetitive mannerisms

DIAGNOSIS

- Laboratory tests: Vitamin B12 and folate deficiency, hypothyroidism.
- Neuroimaging tests: CT scan, MRI scan.
- NINCDS-ADRDA criteria and diagnosis.

NON-PHARMACOLOGIC TREATMENT

- Sleep disturbance, wandering, urinary incontinence, agitation and aggression should be managed with behavioural interventions as possible.
- On initial diagnosis, patient and caregiver educated about course of illness, available treatments, changes in lifestyle that is necessary.

PHARMACOTHERAPY OF COGNITIVE SYMPTOMS

Cholinesterase inhibitors:

- Donepezil, Rivastigmine, Galantamine are indicated for mild to moderate AD, while Donepezil indicated for severe AD.
- Donepezil is piperidine derivative with specificity for inhibition of cholinesterases.
- Rivastigmine has central activity at acetylcholine esterase and butryl cholinesetrases, but low activity at the sites in periphery.
- Galantamine is a cholinesterase inhibitor that also has activity as nicotinic receptor agonist.
- Adverse effects are mild and moderate GI symptoms , urinary incontinence, dizziness, headache, syncope, bradycardia.

Other drugs

Memantine

- It blocks glutaminergic neurotransmission by NMDA receptors, which may prevent excitoxic reaction.

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- It is used as monotherapy and data suggest that when it is combined with a cholinesterase inhibitor, there is improvement in cognition and activities of daily living.
- It is indicated for treatment of moderate to severe AD.
- It is initiated at 5mg/day and increased weekly by 5mg/day to the effective dose of 10mg twice daily.
- Dosing must be adjusted in patients with renal impairment.
- Adverse reactions include constipation, confusion, dizziness and headache.

PHARMACOTHERAPY OF NON COGNITIVE SYMPTOMS

- Cholineserase inhibitors and memantine are first line therapy in early management of behavioral symptoms.
- Antipsychotic medications have traditionally been used to treat disruptive behaviours and psychosis.

PATIENT COUNSELLING

✓ Focus on supporting the patient's abilities and compensating for those abilities he has lost.

✓ Establish an effective communication system with patient and his family to help them adjust to the patient's altered cognitive ability.

✓ Offer emotional support to patient and family and provide safe environment.

✓ Teach them about the disease and refer them to social service and community resources for legal and financial advice and support.

✓ Encourage him to exercise to help maintain mobility.

REFERENCE

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