



RECENT ADVANCES IN THE MANAGEMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a disease of the elderly, mainly affecting people above 60 years of age. It is turning out to be a major public health problem with an estimated 4.7% of the population above 60 years of age (35.6 million) worldwide to be affected by dementia in 2010. The clinical diagnosis is basically a diagnosis of exclusion using various memory tests like MMSE (Mini Mental Score Examination), ADAS-Cog (Alzheimer Disease Assessment Scale - Cognitive domain) to assess the cognitive loss and laboratory tests to rule out other causes of dementia. Imaging procedures like CT, MRI are used to detect the structural changes and PET scans are used to detect the glucose metabolism & amyloid deposits in brain. CSF biomarkers amyloid β_{42} , tau and phosphotau proteins are now used in AD diagnosis the deposition of $A\beta_{42}$ - amyloid plaques in the brain is considered the basic pathology. $A\beta_{42}$ is derived from Amyloid Precursor Protein (APP) by the sequential action of β -secretase and γ -secretase. Pharmacological Management: Only five drugs are approved by FDA for the treatment of alzheimer's disease which are as Cholinesterase inhibitors like Tacrine, Rivastigmine, Donepezil, Galantamine. And NMDA antagonist likes Memantine.

KEYWORDS: Alzheimer's disease cognitive loss Pharmacological Management Imaging procedures



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INTRODUCTION

Alzheimer's Disease (AD) is a progressive neurologic disease of the brain that leads to the irreversible loss of neurons and dementia. The clinical hallmarks of Alzheimer's disease are progressive impairment in memory, judgment, decision making, orientation to physical surroundings, and language. It was first described by German psychiatrist Alois Alzheimer in 1906 and was named after him. Alzheimer's Disease is a disease of the elderly, mainly affecting people above 60 years of age. It is turning out to be a major public health problem with an estimated 4.7% of the population above 60 years of age (35.6 million) worldwide to be affected by dementia in 2010 and it was projected to grow to 115.4 million by 2050; more than 50% of the dementia can be attributed to Alzheimer's disease. The rise in number of dementia patients will be more in the developing countries compared to the developed countries. In India the prevalence of dementia varies from 0.9% to 3.4% of the population above 60 years (1).

Clinical features

The clinical features of Alzheimer's Disease follows a characteristic pattern starting with mild memory impairment and progressing to language and neuropsychiatric symptoms. The various clinical stages are,

- Mild Cognitive Impairment (MCI)
- Mild AD
- Moderate AD
- Severe AD

MCI is defined as memory loss falling below 1.5 SD of the normal population on standard memory tests. In this stage the memory loss is not noticed or attributed to benign forgetfulness. About 50% of MCI patients progress to AD in the next 5 years. In mild AD the memory loss progresses leading to difficulty in learning new facts and poor judgment. In moderate AD the patients develop neuropsychiatric symptoms like depression, agitation & psychosis. There can difficulty in speech (aphasia), inability to do sequential motor activities (apraxia) like dressing, eating, etc. and the daily activities are affected. Some patients lose insight into

the disease (anosognosia). The patients develop delusions in severe AD, cannot identify even close family members and finally become mute and bedridden and are completely dependent on the caregiver.

Diagnosis

The diagnosis of Alzheimer's disease poses a challenge as there is no definite diagnostic test. The definite diagnosis of AD can be made only on biopsy or autopsy demonstrating the typical pathological changes. The criteria for diagnosis are laid down by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's disease and Related Disorders Association (ADRDA) (NINCDS-ADRDA criteria) in 1984 and are updated in 2007 incorporating the recent advances. The criteria given by them are as follows.

- Definite AD - Possible AD with histopathological evidence
- Probable AD - Dementia with typical presentation in the absence of other diseases contributing to dementia.
- Possible AD - Dementia with atypical presentation in the absence of other diseases contributing to dementia.
- Unlikely AD - Dementia of sudden onset or with focal neurological deficits early in course of disease.

The clinical diagnosis is basically a diagnosis of exclusion using various memory tests like MMSE (Mini Mental Score Examination), ADAS-Cog (Alzheimer Disease Assessment Scale - Cognitive domain) to assess the cognitive loss and laboratory tests to rule out other causes of dementia. Imaging procedures like CT, MRI are used to detect the structural changes and PET scans are used to detect the glucose metabolism & amyloid deposits in brain. CSF biomarkers amyloid β_{42} , tau and phosphotau proteins are now used in AD diagnosis¹.

Risk Factors

The risk factors for Alzheimer's Disease are shown in table given below.

Pathology

The pathological hallmark of Alzheimer's Disease is the presence of Amyloid plaques and Neurofibrillary tangles (NFT). There is diffuse atrophy of the cerebral cortex and secondary dilatation of the ventricles. The deposits are found more at the hippocampus, temporal cortex and nucleus basalis of Meynert. There is loss of neurons due to the pathological changes leading on to reduced levels of neurotransmitters especially acetylcholine causing cognitive deficits in these patients². The basic pathological cause of Alzheimer's disease is not fully understood and a lot of research is being done to elucidate the basic pathological process. With the current understanding many hypothesis are put forth for the pathogenesis of AD. The widely accepted among them are,

- Amyloid Cascade Hypothesis
- Tau Hypothesis
- Mitochondrial Cascade Hypothesis

Amyloid Cascade Hypothesis

This is the most widely accepted hypothesis. The deposition of $A\beta_{42}$ - amyloid plaques in the brain is considered the basic pathology. $A\beta_{42}$ is derived from Amyloid Precursor Protein (APP) by the sequential action of β -secretase and γ -secretase. $A\beta_{42}$ is insoluble and aggregates to form plaques which causes oxidative damage and initiates inflammatory processes leading on to neuronal death. There is hyperphosphorylation of tau proteins and their deposition as neurofibrillary tangles secondary to amyloid deposition. Alzheimer's disease occurs in two forms - familial and sporadic forms. Familial forms have an early onset and are associated with mutations in APP gene (chromosome 21), Presenillin-1 (chromosome 14) and Presenillin-2 genes (chromosome 1). The late onset familial form and sporadic forms of AD are associated with the presence of ApoE4 allele. ApoE is involved in cholesterol transport and has three alleles - 2, 3 and 4. ApoE4 allele is present in 40 - 80 % of the alzheimer's patients, though the normal distribution in Caucasian population is only 24 - 30 %. ApoE4 is shown to increase the production and decrease the clearance of amyloid.

Tau Hypothesis

The amyloid cascade hypothesis does not satisfactorily explain sporadic cases of alzheimer's disease and the level of amyloid deposits does not correlate with the degree of cognitive decline. This lead to the Tau hypothesis which asserts that the deposition of tau and formation of neurofibrillary tangles is the basic pathology and the amyloid deposition occurs secondary to it. Tau is a microtubule associated protein which binds to and stabilizes the microtubules involved in intracellular transport. The hyperphosphorylation of tau reduces the binding of tau to microtubules, and the sequestration of hyperphosphorylated tau into neurofibrillary tangles (NFTs) reduces the amount of tau that is available to bind microtubules. As a result the microtubules disintegrate leading to reduced axonal transport and cell death³.

Mitochondrial Cascade Hypothesis

The reduced mitochondrial function to handle the free-radicals is considered the initiating step in alzheimer's disease⁴.

MANAGEMENT OF ALZHEIMER'S DISEASE

Non-Pharmacological Management

A number of nonpharmacologic approaches have been evaluated for improving cognitive functioning in the elderly like regular physical activity, cognitive training like crosswords, puzzles, etc. They are found to effective in reducing the rate of decline of cognitive function. The patients can be given memory aids like notebooks, alarm, etc. to aid in their daily activities. The support provided by the family members play an important role and they should be educated about the disease and care-giving.

Pharmacological Management

Only five drugs are approved by FDA for the treatment of alzheimer's disease which are as follows.

- Cholinesterase inhibitors
- Tacrine
- Rivastigmine
- Donepezil
- Galantamine

- NMDA antagonist
- Memantine

Cholinesterase inhibitors

These drugs inhibit acetylcholinesterase, thereby increasing acetyl choline available at the synaptic junctions. They are used for mild to moderate dementia.

- Donepezil is also used in severe dementia.
- Rivastigmine inhibits butyl cholinesterase also and is approved for use in Parkinson's disease.
- adverse effects were similar to placebo group except for vasogenic edema, a serious adverse event. In ApoE4 allele carriers no statistically significant clinical benefits were observed. Also there was an increased incidence of adverse events compared to placebo group and the frequency of vasogenic edema is more compared to ApoE4 non-carriers⁶.

Phase II trials of pooled purified human IgG against β amyloid showed improved ADAS-Cog & ADCS-CGIC scores. It is now in phase III trials

Anti-aggregatory agents

These drugs act by the unique mechanism of preventing and reversing the fibrilization of β amyloid and reduce the amyloid plaques. *Scyllo-inositol*, a drug with anti-aggregatory action is undergoing phase II trials.

Another drug, *Tramiprosate* (homotaurine) was tried as an anti-aggregatory agent, but its efficacy is not proved in phase III trials and the trials were discontinued. In spite of this, the drug is marketed as an over-the-counter nutraceutical as less reduction in the hippocampal size compared to placebo group was noted in the trials.

RAGE inhibitors

Receptor for Advanced Glycation End products (RAGE) is upregulated on astrocytes and microglial cells in the hippocampus in AD. It is also involved in transport of amyloid across the blood brain barrier. It is postulated that A β binds to RAGE & stimulates the inflammatory cascade. An oral RAGE inhibitor, *PF-04494700* is undergoing phase II trials⁵.

Tau based therapy

These drugs are directed against the tau induced pathological changes in Alzheimer's disease. Most of these drugs are still in preclinical stage of development. Some of the proposed drug targets are

- Hsp90 inhibitors - to increase proteasome degradation of tau
- Tau kinase inhibitors - to reduced hyperphosphorylation
- Microtubule stabilizers - to reduce microtubule disintegration
- Tau assembly inhibitors - to reduce neurofibrillary tangles
- Autophagy enhancers - to increase the clearance of NFTs

Methylene blue

Methylene blue is a histological dye interfering with tau aggregation and promotes its dissolution. In Phase II trials, at the end of 24 weeks, patients on methylene blue did not statistically decline from ADAS-Cog baseline while the control group declined on this score. The decline was 5.5 points in placebo & only 1.5 points in treatment group. At 50 weeks there was a 81% reduction in rate of decline of ADAS-Cog from baseline, relative to the control group. This drug is now in phase III trials.

Davunetide

Davunetide is an eight amino acid peptide (NAP peptide) derived from activity-dependent neuroprotective protein (ADNP) present in brain. It regulates tau phosphorylation thereby inhibiting microtubule disassembly & favours microtubule formation. It is administered intranasally and is currently in phase II trials. The phase II_a trial results has shown a significant improvement in Delayed-Match-To-Sample (DMTS) test by the end of 8 weeks.

Neuroprotective agents

Dimebon is a non-selective antihistamine approved in Russia. It acts by stabilizing mitochondria. Clinical trials have shown a significant improvement in ADAS-Cog, ADCS-ADL, MMSE at end of 26 weeks. It is now in Phase III trials. Anti-oxidants are also being tried as neuroprotective agents⁷.

OTHER DRUGS

- PPAR- γ agonist

Thiazolidinediones

Rosiglitazone & Pioglitazone are used as anti-diabetic agents. They are shown to reduce beta-amyloid accumulation and inflammatory reactants in alzheimer's disease. They may act by enhancing insulin sensitivity. Rosiglitazone & pioglitazone has shown efficacy in clinical trials and are now in phase III trials.

Ginkgo biloba extract - EGb 761(R)

Randomised trials comparing ginkgo biloba extract with donepezil has shown beneficial effects similar to donepezil. Also combination therapy with ginkgo biloba and donepezil is superior to donepezil monotherapy.

Docosahexaenoic acid (DHA)

DHA is a poly unsaturated omega-3-fatty acid showing efficacy in small RCTs. It is currently in Phase III trials.

Statins, Estrogens, NSAIDs

Epidemiological studies has shown reduced risk of alzheimer's disease with use of drugs like statins, estrogens and NSAIDs. But

randomized trials have failed to demonstrate any beneficial role in AD⁸.

SUMMARY

Alzheimer's disease is a progressive neurologic disease leading to the irreversible loss of neurons and dementia. Clinical features start with mild memory deficits and progress to neurological deficits and neuropsychiatric symptoms. There are no definite diagnostic tests for alzheimer's disease and it is a clinical diagnosis of exclusion. The pathological hallmarks of the disease are amyloid plaques and neurofibrillary tangles. The basic pathology of Alzheimer's disease is yet to be clearly understood. The present pharmacological therapy for alzheimer's - cholinesterase inhibitors and NMDA antagonists are lacking in many aspects. The recent advances in understanding the disease process and the increase in the number of patients with alzheimer's disease has paved way for the development of newdrugs at a rapid pace. Some of these drugs show promising beneficial effects in clinical trials and are in the final stages of development.

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