Kathmandu University Medical Journal (2003) Vol. 1, No. 3, 205-211

Review Article

Current Status: Alzheimer's Disease

Ghosh R[1]

[1]Asst. Prof., Dept. of pharmacology, College of Medical Sciences, Bharatpur.

Alzheimer's disease (AD) is a specific type of neurodegenerative dementia characterized clinically by a progressive loss of memory and other aspects of cognition and pathologically by the presence of neurofibrillary tangles, amyloid plaques, and neuronal cell death1. Alois Alzheimer was the first physician to describe the neurohistopathological aspects of AD in 1907 in a 55-year-old woman. It accounts for 50-60% of the causes of senile dementia. However, it has become clear that AD can occur in any decade of adulthood and is the most common cause of dementia in the elderly. 20- 15% of the population over age 65 and almost 50% of the population over 85 has some degree of dementia2. There are considerable medical, financial, social and emotional costs associated with the burden of caring for patients with AD.

Pathophysiology of AD

The exact pathophysiology of AD is still unsettled. The different risk factors for development of AD are: old age, female gender, family history of dementia, ApoE ε4 allele (in non familial AD), lower educational attainment, head trauma with loss of consciousness, thyroid dysfunction, no post-menopausal-estrogen therapy, different environmental factors like aluminium, mercury, viruses, prions etc, inflammation of the brain and Down's syndrome[3,4,5].

Early changes in AD include atrophy of the hippocampus and entorhinal cortex. There is loss of cholinergic and other neurons in the cerebral cortex and nucleus basalis of Meynert and related nuclei that contain the cell bodies of cholinergic neurons which project to hippocampus, amygdala and all of the neocortex[2]. Reduction in nicotinic cholinergic receptors is reports in AD. It is likely that 4 containing nicotinic receptor subtypes are reduced predominantly in Ad[6].

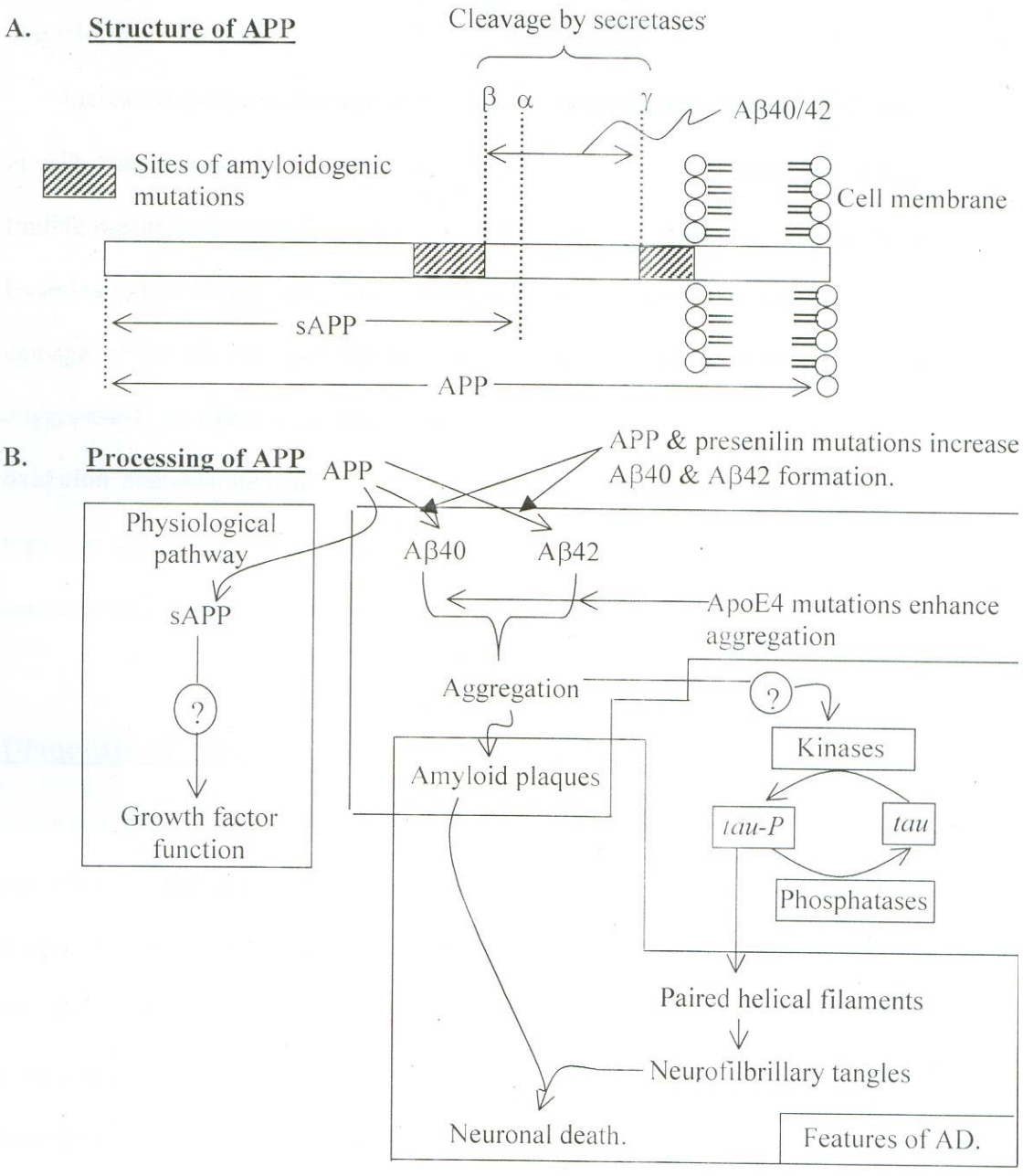
The cause of the neuronal degeneration in AD is still not confirmed. The cytopathologic hallmarks of the disease are intracellular NEUROFIBRILLARY TANGLES and extracellular NEURITIC SENILE PLAQUES. Neurofibrillary tangles are made up in part of hyperphosphorylated forms of the tau protein that normally binds to microtubules. The neuritic plaques contain a central core that includes β – amyloid (Aβ), ApoE, proteoglycans and other proteins. Aβ is a 4.2-k Da protein of 39 – 42 amino acids that is derived proteolytically from amyloid precursor protein (APP) by the enzymes α, β and γ secretases. Two types of Aβ are found – Aβ-40 and Aβ42 forms insoluble aggregates[4,7].

There are two proteins found in the membranes of cellular organelles: Presenilin-1 (coded by a gene on chromosome 14) and Presenilin-2 (coded by a gene on chromosome I). Both the Presenilins are related to γ-secretase activity for Aβ synthesis. About 50% of cases of early onset AD have mutations in the genes – chromosome 14 and chromosome 1. Mutations of the gene on chromosome that codes for APP are also associated with early onset AD. It is interesting in this regard that patients with Down's syndrome have an extra chromosome 21 (trisomy 21), and they are known to develop dementia of the Alzheimer type[2].

Furthermore, there is a correlation between the isoforms of apolipoprotein E (apoE) and age of onset of AD. The gene for this protein, which is on chromosome 19, produces three major isoforms: ε2, ε3 and ε4. The ε4 allele of apo-E shows strong association with Ad in the general population, including sporadic & late onset familial cases4. It has been suggested that apoE may be involved in the transport of processing of the APP.

Correspondence
Dr. Ranjib Ghosh
Asst. Professor, Dept. of Pharmacology,
College of Medical Sciences, Bharatpur, Nepal.
E-mail: ghoshranjib@rediffmail.com

Figure 1:- Pathogenesis of AD[9]



A] Structure of APP, showing origin of secreted APP (SAPP) and Aβ-amyloid protein. The regions involved in amyloidogenic mutations discovered in some cases of familial AD are shown flanking the Aβ sequence. APP cleavage involves 3 proteases, secretases α, β and γ. Secretase α produces soluble APP, whereas secretases β & γ generated Aβ amyloid protein. An altered balance between these enzymes may be a factor in amyloidogeneis.

B] Processing of APP. The main "physiological" pathway gives rise to sAPP, which exerts a number of trophic functions. Cleavage of APP at different sites gives rise to Aβ, the predominant form normally being Aβ40, which is weakly amyloidogenic,

mutations in APP or presenilins increase the proportion of APP which is degraded via the amyloidogenic pathway, an also increase the proportion converted to the much more strongly amyloidogenic form Aβ42. Aggregation of Aβ is favoured by mutations in the apoE4 gene do bind better to Aβ than other forms of apoE and may thus contribute to enhanced amyloid fibril formation[7].

Increased oxidative damage also is a prominent and early feature of vulnerable neurons in AD. But, a major limitation in determining the source of oxidative damage, as well as finding means to attest this damage, is paucity of cellular models directly homologous to AD. Examination of biopsy specimens of the olfactory epithelium revealed increased oxidative damage of the neurons and the surrounding epithelial cells. Lipid peroxidation and hemeoxygenase-I, a stress response protein, were increased, while nucleic acid or protein oxidation demonstrated in vulnerable neurons in AD were not increase. These findings highlight the systemic nature of oxidative abnormalities in AD, but the different cell types may express this abnormality by a different array of oxidative stress-markers[8].

Diagnosis of AD:- Arriving at a clinical diagnosis of AD seems closer to an art than a science, considering the complexity of clinical manifestations, the incomplete history from a caregiver and the lack of diagnostic marker with adequate specificity for the disease. Clinical diagnosis of AD even in the hands of dementia specialists is confirmed at autopsy 80 – 90% of the time. The 10 – 20% misdiagnosed cases have pathological evidence of another neurological conditions[4,7]. The diagnosis of Ad is based on careful clinical assessment of the patient and appropriate laboratory test to exclude other disorders that may mimic AD; at present no direct ante mortem confirmatory test exists[10]. Slowly progressive decline in memory and orientation, normal results on laboratory test, and an MRI or CT scan showing only diffuse cortical atrophy including the hippocampus is highly suggestive of AD. Research studies have indicated a general decrease in CSF Aβ levels with an increase in tau protein. The use of blood apolipoprotein E genotyping for diagnosis of AD is under investigation[4].

Table: 1 Diagnostic features of dementia of Alzheimer's type[1,3,4]

A] **Gradual and continuing decline of cognitive functions**

1. Loss of recent memory
2. One or more of the following cognitive disturbances:
   a. aphasia (language disturbance)
   b. apraxia (impaired ability to carry out motor activities despite intact motor function)
   c. agnosia (failure to recognize or identify objects despite intact sensory function)
   d. disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting etc.)

B] **Behavioral disturbance:** At some pint during the illness a majority of patients will exhibit one or more of the following behavioral disturbances: agitation, delirium, delusions, psychosis, emotional liability and depression, sleep disturbance and night time wandering etc. In later stages of the disease muscle rigidity and even seizure may develop.

C] **The cognitive deficits in criteria A1 and A2 are not due to any of the following:**

1. Other CNS conditions that cause progressive deficits in memory and cognition (e.g. cerebro-vascular disease, Parkinson's disease, subdural hematoma, normal pressure hydrocephalus, brain tumour etc.)
2. Systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection etc.)
3. Substance induced conditions.

Management:- Presently available pharmacological treatments for AD are symptomatic and do not alter the course or progression of the underlying disease. Current management focuses on establishing an accurate clinical diagnosis, around the clock care of the patient, supporting caregivers and treating associated non-cognitive problems[11]. However , there are avenues for development of new therapies, which will hopefully be directed towards improvement of cognitive function[12]. In general, appropriate management of AD patients with antioxidants, acetylcholinesterase inhibitors and psychotropic agents can slow the progression of the disease, improve cognition, and reduce behavioral disturbances, which may enhance patient and care-giver quality of life and delay nursing home admission[13].

Management of AD can be divided into the following headings:

A. Pharmacotherapy for improvement of cognitive functions.
B. Pharmacotherapy for behavioural disturbances.
C. General measures.

A] Pharmacotherapy for improvement of cognitive functions:

I. **Cholinergic therapy:-** A major approach to the treatment of AD is to augment the cholinergic functions. Different cholinesterase inhibitors or cholinergic agonists are already approved or under clinical trial for the treatment of AD.

1. **Tacrine:-** It is an acridine derivative ad a centrally acting cholinesterase inhibitor. It is labelled for the treatment of mild to moderate Ad. Dosage over 120mg/day is effective in decreasing cognitive defects in 60% of patients. However 20% of the patients receiving tacrine develop reversible hepatic enzyme elevation.
2. **Donepozil:** It is a centrally acting cholinesterase inhibitor. It is not hepatotoxic and can be administered at a dose of 5-10 mg once dialy[4].
3. **Rivastigmine:-** It is a centrally acting anti-cholinesterase. In clinical trials, at a dose of 6-12mg/day rivastigmine has shown improvement in cognitive functions in 81% of the cases at 26th week as compared to placebo treated patients. Patients treated with rivastigmine demonstrated significant improvement in total word recall and recognition, orientation and ability to speak [14].
4. **Galantamine**: Originally it is derived from daffodil bulb. In addition to blocking the action of acetylcholinesterase enzyme, this drug appears to act on brain's nicotinic receptors. The modulations of these receptors can lead to the release of acetylcholine and amplify cholinergic transmission. Clinical trials have shown that treatment with galantamine produces significant and sustained benefit in cognition, global function and delay in emergence of behavioural disturbances in Ad patients[14].

Donepozil, rivastigmine and galantamine are approved by FDA for the use in the treatment of AD[15]. Mamantine, another acetylcholinesterase inhibitor has shown benefit in clinical trials in moderate to severe dementia, although it is not yet approved by FDA[16]. They also improve non-cognitive symptoms such as psychosis & apathy. Both efficacy and side effects are similar between these compounds[11]. The dose related side effects are nausea, vomiting, diarrhoea, bradycardia and dizziness. Even without actual improvement, these agents may provide stabilization of the patients' conditions for a period of months. There is no evidence that these drugs are beneficial in the late stage of the disease. Contraindication for cholinesterase inhibitors include liver disease, alcoholism, peptic ulcer disease, chronic obstructive pulmonary disease and bradycardia[11,14].

5. Newer cholinergic therapy of possible benefit in the treatment of AD & their current status are shown in table II.

Table II. Newer cholinergic therapy in AD[14].

Drug	Status	Mechanism of action
Epastigmine	Phase 3 clinical trial	Cholinesterase inhibitor
Physostigmine sustained release formulation	Phase 3 clinical trial	Cholinesterase inhibitor
Metrifonate	Phase 3 clinical trial	Cholinesterase inhibitor
Xanomaline patch form	Phase 2 clinical trial	Cholinergic agonist
Milameline	Phase 3 clinical trial	Cholinergic agonist
AF 102B	Phase 3 clinical trial	Cholinergic agonist
SB 202026	Phase 3 clinical trial	Cholinergic agonist

II. Other therapeutic approaches:-

1. **Estrogen therapy:-** Estrogen replacement therapy have shown about 50% protection against development of AD in women. Estrogen may also be protective in A in man, besides its effect on bone, cardiovascular system and prostate gland17. The mechanism of possible estrogen effects on AD is unknown but may result from direct effects on cholinergic neurons, antioxidant properties, or lowering levels of apoE[4].

2. **Ginkgo-biloba:-** Ginko-biloba was found to produce improvement in cognitive functions in subjects of Ad in clinical trail. But it requires further confirmation for its use in the treatment of AD[4].

3. **Non steroidal anti-inflammatory drugs (NSAIDS):-** Since it has been reported that inflammatory processes are associated with the pathophysiology of several neurodegenerative diseases and the NSAIDS inhibit amyloid-beta protein induced neurotoxicity to reduce the risk of AD, a number of studies have been conducted focusing on the neuroprotective effects of NSAIDS. The neuroprotective effects of these drugs are not related to their cyclooxygenase (COX) – inhibiting property[18]. High dose aspirin shows better protection and better maintenance of cognitive functions that the low dose aspirin and other NSAIDS like paracetamol and dpropoxyphene[19]. Different prospective studies regarding the role of NSAIDS in Ad are in progress at present [4,9].

4. **Other agents under investigations:-** Different antioxidants (like vitamin E, selegeline, phenyl-a-tert-buty1 nitrone, EUK-8), B-blockers (propranolol, pindolol), clonoidine, guanfacine, nimidipine, ergoloid mesylates, nicotine etc are under investigation for the treatment of AD[14]. Weekly immunization with AB peptide in an APP mutation mouse model both prevented and reversed the accumulation of amyloid plaque in the brain. inhibition of the enzyme APP B secretase might decrease the amyloid accumulation in brain & this may be an important therapeutic strategy for AD[4]. The role of apoptosis in AD is most debated. This implies that little is known about the potentially involved pathways. Moreover, there is lack of suitable animal models for drug evaluation. Much remain to be done in this area to explore the potential role of antiapoptotic drugs in the treatment of AD[20].

B] Pharmacotherapy for behavioural disturbances:- although the core feature of all types of dementia is progressive cognitive disruption, most of the patients also express noncognitive behavioural problems. These noncognitive problems lead to potentially devastating disabilities, and often a major cause of stress, anxiety and concern for caregivers. So the associated behavioural disturbances of the patient should also be treated adequately. For example, selective serotonin reuptake inhibitor (SSRIs) or tricyclic antidepressants (TCAs) with low anti-cholinergic side effects (desipramine, nortriptyline) can be used as antidepressants. Generalized seizures should be treated with an anticonvulsant like phenytoin or carbamazepine. Agitation should be treated with haloperidol, risperidone and benzodiazepines (such as lorazepam). But these medications frequently have unwanted side effects like sedation, confusion, increased muscle tone, fall and adventitious movements. Low dose haloperidol (0.5 to 2mg), trazodone, buspirone, propranolol and olanzapine may be the most helpful and have the fewest side effects[4,21].

C] General measures:- A number of general environmental and behavioural management principles can optimise safety, enhance function, and thus delay hospitalisation. Familiar physical surroundings, simple and constant daily routine, door

locks to prevent wandering, protections against hot stove surfaces & toxic substances and avoidance of driving are all important safety measures. Loss of independence and change of environment may worsen confusion, agitation and anger. Proper communication to the patients and other general measures to help the patients, especially in the late stage of the disease by the caregivers are all the necessary. Different organizations should come forward for the help of such patients suffering from dementia. The Palliative Excellence in Alzheimer's Care Effort (PEACE) program in United States is a disease management model for dementia that incorporates advance planning; patient cantered care, family support, and a palliative care focus from the diagnosis of dementia through its terminal stages.

Conclusion

A cure of AD is till far off, and clinicians face the burden of caring for patients at all stages of dementia for the foreseeable future. Those with advanced disease suffer neurological symptoms and signs like incontinence; problems with gait and mobility; marked cognitive, language, and functional impairment; and in about 90% of patients, significant behaviour problems. Whether patients are resident in the community or living in the nursing home, this composite reflects a highly complex medical and neuropsychiatric management challenge. Clinicians can better address these problems with awareness of current treatment options. Emerging data have expanded physicians' ability to use pharmacotherapy in patients with advanced dementia. Physicians need to enact the principle that something can be done for our afflicted parents and grandparents.

References

1. Clark MC, Arnold SE, Alzheimer's Disease, In: Rakel RE(ed.), Conn's Current Therapy. Philadelphia: WB Saunders company. 1997; 872-877.
2. Ganogn FW (ed.), Higher functions of the Nervous system: Condition reflexes, Learning, & Related phenomena. Review of Medical Physiology. 20th ed. New York : Mc Graw Hill. 2002 ; 263-264
3. Kalplan HI, Sadock BJ (eds). Dementia. In : Kaplan and Sadock's Synopsis of Psychiatry. 8th ed. Baltimore: Williams & Wilkins. 1997;328-345.
4. Bird TD. Alzeheimer's Disease. And Other Primary Dementias. In : Braunwald E, Fauci As. Kasper Dl, Hauser Sl, Londo Dl, Jameson JL (eds.). Harrison's Principles of Internal Medicine. 15th ed. New York: McGraw Hill. 2001; 2391-2395.
5. Fukumoto H, Ingelsson M, Garevik N, Wahlund LO, Nukina N, Yaguchi Y. ApoE varepsilon 3/ varepsilon 4 heterozygotes have an elevated proportion of apolipoprotein E4 in cerebrospinal fluid relative to plasma, independent of Alzheimer's disease diagnosis. Exp Neurol. 2003; 183(1): 249 –253.
6. Graham AJ, Martin-Ruiz CM, Teaktong T, Ray MA, Court JA. Human Brain Nicotinic Receptors, their distribution and participation in neuropsychiatric disorders. Curr Drug Target CNS Neurol Disord. 2002;1(40: 387-397.
7. Kumar V, Cotron RS, Robbind Sl (eds.). Alzheimer's Disease. In: Basic Pathology. 6th ed. Singapore: Harcourt Asia PTE Ltd, 2001; 739-740.
8. Perry G, Castellani RJ, snith MA, Harris PL, Kubat Z, Ghamabari K. Oxidative damage in the olfactory system in Alzheimer's disease. Acta Neuropathol. 2003; 4(2): 112-115.
9. Rang HP, Dale MM, Ritter JM (eds.). Neurodegenerative disorders: Alzheimer's Disease. Pharmacology. 4th ed. Edinburg: Churchill Livingstone. 1999; 504-507.
10. Standaert DG, Young AB. Treatment of Central Nervous System Degenerative Disorders. In Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, gilman AG (eds). Goodman Gilman's The Pharmacological Basic of Therapeutics. New York: McGraw Hill. 1996;503-519.
11. O'Biren JT, Ballard CG. Drugs for Alzheimer's Disease. BMJ. 2001; 17(8): 678-681.
12. Marwah B. Advances in Drug Treatment of Alzheimer's Disease. Drugs: News and Views. 1995;3(2): 115 – 118.
13. Akhondzadeh S, Norooozian M. Alzheimer's disease: Pathophysiology and Pharmacotherapy. I Drugs. 2002; 5(11): 1062 – 1069.
14. Balaraman R. New Drugs for Alzheimer's Disease. Ind J of Pharmacol. 2001; 33:118-119.
15. Cacabelos R, Alvarez A, Lombardi V, Ferandez NL, Corozol L, Perez P. Pharmacological treatment of Alzheimer's disease: From psychotropic drugs and cholinesterase inhibitors to pharmacogenomics. Drugs Today. 2000; 36(7): 415 – 499.
16. Tariot PN. Medical management of advanced dementia. J Am Geriatr Soc. 2003; 51:305-313.
17. Gooren LJ, Toorians Aw. Significance of estrogen in male pathophysiology. Ann Endocrinol. 2003; 64(2): 126-135.
18. Asanuma M, Miyazaki I, Tsuji T, Ogawa N. New aspects of neuroprotective effects of nonsteroidal anti-inflammatory drugs. Nihon

shinkei Seishin Yakurigaku Zasshi. 2003; 23(3): 111-119.
19. Nilsson SE, Johansson B, Takkinen S, Berg S, Zarit S, McClearn G, Melander A. Does aspirin protect against Alzheimer's dementia? A study in Swedish population-based sample aged>/=80 years. Eur J Clin Pharmacol. 2003; 59(4): 313-319.
20. Waldmeier PC. Prospects for antiapoptotic drug therapy of neurodegenerative disease. Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27(2): 303 – 321.
21. Moretti R, Torre P, Antoenello RM, Cazzato G, Friggo S, Bava A. Olanzapine as a treatment of neuropsychiatric disorders of Alzheimer's disease and other dementias: a 24-month follow up of 68 patients. Am J Alzheimer's Dis Other Demen. 2003; 18(4): 205 –214.