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Review Article

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Alzheimer 's disease - Recent Advancement in Neuroscience Research

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ABSTRACT

Alzheimer's disease also known as dementia is one of the widely affective neurodegenerative disorder only after Parkinsonism. The patients suffering from Alzheimer's disease has increased dramatically over a period of time. This has propelled the interest of neuroscientists to develop new drug therapies to combat this disease. The drugs available are not effective in permanently curing the disease, but effective in mostly reducing the symptoms of the disease and delaying its progression. This review has been produced by probing relevant publications, PubMed and Medline articles. The Pharmacotherapy revolves around two drugs, Acetylcholinesterase Inhibitors which are most effective in treating mild, moderate and severe form of Alzheimer's disease. The other drug being Memantine, NMDA receptor antagonist which has been effective in combination with Acetylcholinesterase Inhibitors in moderate to severe form of Alzheimer's disease. The underlying pathophysiology of Alzheimer's disease is not very clear. Contemporarily there has been alarming advancements in the pathophysiology of Alzheimer's disease which provided the gateway for neuroscience research in determining the most favourable investigational treatments which includes Passive and Active immunization techniques against Amyloid-β-protein and development of β and γ secretase inhibitors.

KEY WORDS

Alzheimer's disease, Dementia, Memantine, Neuroscience, Acetyl cholinesterase.

INTRODUCTION

Wilkins RH and Brody IA (1969), in his paper described Alzheimer's disease getting its name after German Physician, Alois Alzheimer who described the disease (1). This disease has been a foremost public health issue affecting almost 5 million individuals in USA. The majority of the patients are elderly individuals in ages 65-95 years (2).

Bird TD, *et al.* (2007) has defined in his book that dementia is an acquired disease wherein the patient cognitive ability and activities of daily living (ADL) is impaired (3). The risk factors are the increasing age and memory loss (3).

Epidemiology and Genetics

Gao S, *et al.* (1998) has reported relationship between age, sex and incidence of dementia and Alzheimer's disease, stating that the increasing age is the major risk factor for Alzheimer's disease (AD) with the frequency expanding every 5 years between ages 65-95 years and increasing 2% at 65 years of age and to 40% over 85 years of age (2).Duijn VC, *et al.* (1991) has conducted a case study and described that rarely dementia occurred in age group of 20-30 years individuals. He also stated that until the age of 50 years the inception of clinical symptoms is uncommon (4). It was also reported in his study that family history plays an important role in development of AD. Individuals having first degree relatives are 3-4 times more prone to get AD among

individuals having two or more first degree relatives (4).

Brunkan AL and Goate AM (2005) has presented a paper on Presinilin function and gamma secretase activity, stating the onset of Familial AD is due to genetic mutations in the 21, 14 and 1 pair of chromosomes which would result in abnormal precursor proteins Presinilin 1 and Presinilin 2 which together acts in a multifaceted manner as γ-secretase (5). Goedert M and Spillantini MG (2006) in his article "A century of Alzheimer's disease" reported augmented levels of Amyloid-β-protein in genetic mutated patients (6).

Tsai MS, *et al.* (1994) in his article defined that the presence of Apolipoprotein A on chromosome 19 as important risk factors for the development of late onset AD (7). Gender education, head trauma, memory deficit and small hippocampal volume contribute towards risk factors for the development of AD.

Rapp SR, *et al.* (2003) and Shumaker SA, *et al.* (2003) has pointed out in their study that the replacement of oestrogen may enhance the susceptibility to AD (8, 9). Schmand B, *et al.* (1997) has pointed out the fact that educating individuals imparts "Cognitive Reserve" which delays the occurrence of AD (10). Martins IJ, *et al.* (2006) has established the fact that there is a correlation metabolic syndrome and vascular risk factors increasing the susceptibility of AD (11). Sidera C, *et al.* (2005) and Moreira PI, *et al.* (2007) has stated that high cholesterol, obesity, hypertension, diabetes mellitus are implicating factors for AD (12, 13).

Pathophysiology

Dementia has been characterised by the loss of neuronal network between various parts of brain. Cummings JL, *et al.* (1998) pointed out in his article that AD is also characterised by reduction in synaptosomes density due to loss of larger neurons from superficial cortex region (14). The most alarming development came from Francis PT, *et al.* (1999) paper regarding the cholinergic hypothesis of Alzheimer's disease. He stated that the cholinergic neurons are essential for memory function and loss of these neurons would lead to loss in memory functional capacity of individuals (15). The anatomical neuronal network of AD starts from the Entorhinal cortex region of brain and progresses to Hippocampus, the posterior and temporal cortical regions. This points the fact that cerebral cortex as an important region for the development of AD. The atrophy of the cortex would lead to loss and contract neurons leading to AD. Braak H and Braak E(1991) & Squire LR and Zola-Morgans S (1991) have confirmed the fact impaired medial temporal lobe would lead to AD (16, 17). Microscopical evidence of AD implicated that neurofibrillary tangles and amyloid plaques are two important ascertaining features of AD. Hardy J and Selkoe DJ (2002) has pointed out the Amyloid Hypothesis attributes towards the origin of AD (18). The progression of AD would lead to Noradrenergic, Glutaminergic and Seratonergic system deficiencies which would further aggravate the cognition and behaviour.

History

Wixted JT (2004) has described in his paper the Ribot's Law of retrograde amnesia, describing that the short term memory is influenced more likely when compared to Long term memory in AD patients. The long term memory deteriorates over the period of time in AD patients (19). Dujin, *et al.* (1991) has described in his article that the Mild cognitive impairment patients progresses to AD dementia eventually with an advancement rate of 12% for 1 year (4). The progression towards AD is rapid with patients having pre-existing cognitive impairment. The advanced stage symptoms of AD include delusions, agitation, paranoia, anxiety and

insomnia. Yesavage (2002) has reported in his article the sleep-wake cycle disturbance in Alzheimer's disease, the frequent sleep disturbance in night, daytime sleepiness and early morning awakening (20).

DIAGNOSIS

Diagnostic Manual of Mental Disorders, Fourth Edition (DSM-IV)(21) & *National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRNA)*(22) has been most important clinical criteria for the development of AD. Various neuropsychological tests have been determined for the diagnosis of AD. The *Mini Mental State Examination (MMSE) & Community Screening Instrument for Dementia (CSI-D)* has been widely used as screening instruments for AD (23, 24).

There have been normal neurological examinations in patients diagnosed with AD. Currently there are no diagnostic tests to determine AD. The current tests are propagated from the *National Institute on Aging (NIA) & National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)* which involves detection of neocortical plaque densities which are age-adjustable (25). *The Consortium to establish a Registry for Alzheimer's disease (CERAD)* necessitates the need of age-adjusted semi quantitative plaque frequency and clinical diagnosis for AD (26).

DuBois B, *et al.* (2007) paper on research criteria for the diagnosis of Alzheimer's disease has pointed the recent advancement in the technical acquaintance leading to development of reliable biomarkers on basis of structural Magnetic Resonance Imaging (MRI), molecular imaging with Positron Emission Tomography (PET) and Cerebrospinal fluid analysis (27). Structural MRI analysis in AD patients spectacles atrophy in hippocampus and entorhinal cortex region which is extrapolative of future cognitive study.

MRI volumetry is also an imaging attachment for the diagnosis of AD (28, 29).

Fluorine labelled FDG-PET brain images shows decrease in glucose metabolism. This has been ascribed as major diagnostic adjunct for AD. The other radiotracers like Carbon-11 have increased application of PET for the diagnosis of dementia and AD (30). The conjuring up of amyloid or tau protein is one of the recent advancements for the early diagnosis of AD. Thus PET imaging diagnosis will be the future research focus for the development of various radiotracers and molecular targets.

TREATMENT

The treatment of AD has been far long major area of discussion. The drugs available for the treatment of AD mostly delay the disease progression in affected individuals (31). Lately no therapy has been developed which could cure the disease completely and eradicate the behavioral and neurological problems. The acetyl cholinesterase inhibitors mostly improve the behavioral symptoms, cognitive function and global functionality (32). Haley WE (1997) has highlighted the role of the caregiver as critical in determining the right drug and dosage in treatment of AD (33).

Many drugs have been developed lately for the treatment of AD. The major pharmacotherapy for AD can be categorised into two,

a) Symptomatic approach by increasing the neurotransmitter release.
b) Neuroprotective approach by using antioxidants such as Vitamin E.

Yaari R and Corey-Bloom J (2007) have stated in his paper that the AD patients are given Antidepressants and Antipsychotics to manage the behavioral and psychiatric symptoms (34).

The first important effective medications for AD are the Acetyl cholinesterase inhibitors which increase the concentration of Acetyl choline in the synaptosomes by preventing the degradation of Acetyl choline thus beneficial for AD patients as they are deficient of Acetyl choline in brain. They are 4 important AChE inhibitors approved by FDA, Donepezil, Tacrine, Rivastigmine and Galantamine. These drugs were effective in improving the symptoms, behavioral and cognitive abilities inspite of their cost-effectiveness and toxicity profile (35, 36).

The second important effective medication for moderate to severe AD approved by FDA is Memantine, NMDA receptor antagonist (37). Memantine acts by antagonising the activity of glutamate at the NMDA receptor thus improving signal transduction and reduces the excess flow of calcium ions preventing the destruction of the cholinergic system. The drug was effective in improving the cognitive and behavioral ability in AD patient (38). Atri A, *et al.* (2008) highlighted the combination therapy of AChE inhibitors and Memantine worked well for AD patients with impairment of cognitive and behaviour abilities in contrast to the AChE or Mematine therapy alone (38).

Sano M, *et al.* (1997) has highlighted the role of antioxidants in the pathology of AD (Sano 39). He found that the Vitamin E (α-tocopherol) and Selegiline have been effective in treatment of AD patients (39). Aisen PS, *et al.* (2003) & Mailard M and Burnier M (2006) highlighted the role of NSAID's in treatment of AD patients and pointed out that these drugs had greater threats than benefits (40, 41).

Risperidone and Olanzapine are the two drugs approved by FDA in the management of the behavioral symptoms in AD. Selective serotonin reuptake inhibitors have been shown to be moderately effective in the management of the behavioral symptoms in AD.

Future advancement in Neuroscience research in AD drug therapy

Roberson ED and Mucke L (2006) had stated that new drugs have been evaluated for the clinical effectiveness in the treatment of AD. (31). The prominence is mostly on approaches to allay the toxicity of β-amyloid protein (42). Vaccination against AD has also been developed but the trials were stopped due to subjects developed encepahalitis (42).

CONCLUSIONS

Recently there have been developing novel treatment strategies in treatment of AD and associated symptoms. The progress is at snail's pace but evident development has been produced in the pathophysiology of AD which gives the neuroscientists room for evolving new drug therapies in treatment of AD.

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