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THERAPEUTIC APPROACHES IN THE TREATMENT OF ALZHEIMER'S DISEASE: A REVIEW

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ABSTRACT

The incidence of Alzheimer's disease (AD) in ageing populations (above 65 years of age) has never been greater and is expected to increase substantially in the next decades ahead. Hence, there is an urgent need to develop safer and more efficacious drugs to help combat the tremendous increase in disease burden. However, the effective management of AD has been a challenging area of research interest for scientists all over the world as no complete cure has been achieved yet. Better understanding of neurological basis, etiology and pathophysiology have certainly raised hopes in finding better pharmacotherapies but have been examined in very few patients to come to a concrete conclusion. This article reviews the current therapeutic approaches used in the management of AD. The various approaches discussed here include cholinergic hypothesis, hormone replacement, anti-inflammatory drugs, neurotropins, neuroprotectives, inhibition of amyloid formation, anti-oxidants and NMDA receptor antagonists.

KEYWORDS: *Alzheimer's disease, Amyloid cascade, Neuro fibrillary tangles.*

INTRODUCTION

Alzheimer's disease (AD) is one form of dementia, which is characterized by progressive degenerative brain disorder that gradually destroys a person's thinking, language, behavior and ability to learn reason, make judgments, communicate, and carry out daily activities. It primarily affects the elderly population and is estimated to account for 50% to 60% of dementia cases in people over 60 years of age. [1]

The main symptoms associated with AD include:

- Cognitive dysfunction, primarily memory loss
- Language deficits
- Depression
- Behaviour problem including agitation, mood disturbances, Psychosis [2, 3]

Neuropathology of AD:

In the neuropathology of AD, there is an overall shrinkage of brain tissue. The sulci are noticeably widened and there is shrinkage of the gyri. In addition, the ventricles that contain the cerebrospinal fluid (CSF) are noticeably enlarged. [4]. There are abnormal degenerative structures called neuritic plaques (extracellular lesions consisting of ß-amyloid) and neurofibrillary tangles (consisting largely of a type of abnormally phosphorylated protein twisted together into bundles called tau proteins) [5]. The deposition of ß-amyloid destroys the neuron. In some patients, there is abnormality in the DNA that code for the protein called amyloid precursor protein (APP). The abnormal DNA starts lethal chemical cascade in neurons, beginning with the formation of altered APP, which leads to the formation of ß-amyloid deposits. The next step is that ß-amyloid deposits form plaques and tangles in the neuron which indicates cell damage and cell death, which if sufficient gives rise to formation of the symptoms in AD.

Another possible mechanism could be that there is an unexplained defect in the working of the protein called apolipoprotein-E (APO-E), which binds to amyloid and removes it.[6]
APO-E is a multifunctional protein involved in lipid metabolism and neurobiology. Its gene (ApoE) has three common isoforms (ApoE2, ApoE3, and ApoE4) with different effects on lipid homeostasis and neurobiology. Unlike ApoE3, the most common isoform, ApoE4 is associated with increased risk of developing AD and other neurodegenerative disorders. [7]

Furthermore, apoptotic cell death mechanisms play an important role in neuronal cell death in AD. Under different experimental conditions (at baseline or after in vitro incubation in the presence of proapoptotic stimuli) increased levels of apoptosis and enhanced caspase- 3 (any of a group of proteases that mediate apoptosis) activity were detected in lymphocytes from AD patients. [8]

Differential Diagnosis:

The challenge to a physician, while diagnosing the disease, is to look for the alternative conditions which are possible. From the point of view of diagnosing Alzheimer's disease, those conditions include Pseudodementia and delirium.[9] In early stages of the disease, other etiologies of dementia should be excluded. These include treatable entities such as thyroid disease, vitamin deficiencies, brain tumor, drug and medication intoxication, chronic infection, and severe depression. Neuroimaging studies (CT and MRI) do not show a single disease. As AD progresses, diffuse cortical atrophy becomes apparent, and MRI scans show atrophy of the hippocampus. Imaging helps to exclude other disorders, such as primary and secondary neoplasms, multi- infarct dementia, diffuse with matter disease, and NPH; it also helps to distinguish AD from other degenerative disorders with distinctive imaging patterns such as FTD or CJD. Functional imaging studies in AD reveal hypoperfusion or hypometabolism in the posterior temporal-parietal cortex. The EEG in AD is normal or shows nonspecific slowing. Routine spinal fluid examination is also normal. CSF Aß amyloid levels are reduced whereas levels of tau are increased, but the considerable overlap of these levels with those of normal aged population limits the usefulness of these measurements in diagnosis. Slowly progressive decline in memory and orientation, normal results on laboratory tests, and an MRI or CT scan showing only diffuse or posteriorly predominant cortical and hippocampal atrophy is highly suggestive of AD. [10]

Causes and risk factors:

- Age: As the age increases from 65-79 years, the risk of AD increases from 1.5% to 6.8%. Risk of AD nearly doubles every 5 years beyond the age of 65. [11]
- Family history: Having a parent or sibling with AD increases the risk by 2 or 3 times. [11]
- Genetic causes: Gene identified so far for the late onset AD is ApoE that makes protein APOE. [11] Mutations on chromosomes 1, 14, 21 increase the risk of getting AD. ApoE gene variants on chromosome 19 may possibly contribute to cause late onset AD. Less than 1% of all cases of AD are due to a chromosomal defect called trisomy 21 (also known as Down syndrome) The APP gene, which encodes the amyloid precursor protein is localized on chromosome 21. Thus it is felt that people with Down syndrome overproduce this protein resulting in its accumulation.[12]

- Estrogen: Women have an increased risk of AD due to loss of estrogen following the menopause which influences several brain process predicted to modify risk of AD. Effects of estrogen on oxidative stress, inflammation and cerebral vasculature may ameliorate the risk.[13]

- Environmental causes: The environmental agents such as diet, aluminum, and viruses are important causative factors. These may increase the prevalence of AD by eliciting inflammation, which may cause the neurological damage which results in AD. [14]

TREATMENT

A complete cure is still not available. But drugs that aim at slow progression of the disease or which treat the symptoms are available.

Therapeutic approaches for the treatment of Alzheimer's disease:

AD should be distinguished from other forms of dementia. In some cases, depression can result in dementia-like symptoms. Other examples include chronic drug use, chronic infections of the CNS, thyroid disease, and vitamin deficiencies. These causes of dementia can often be treated. It is, therefore, important to obtain an accurate diagnosis to avoid complications associated with the inappropriate treatment and long-term care of these patients.

Treatment of AD is mainly palliative and focuses on mitigating symptoms. Each symptom is treated based on its severity and other symptoms that are affecting the individual. Most of AD patients will eventually need professional care in assisted living or nursing homes. They require constant supervision as memory loss becomes incapacitating. There are several pharmacological interventions and treatment regimens that are suggested. In the last few decades different hypothesis and approaches were proposed for the treatment of AD. These [12] include cholinergic hypothesis, hormone replacement approach, anti-inflammatory approach, neurtropins, agents stimulating neurotrophic effects, inhibition of amyloid formation and neurofibrillary tangles, antioxidants and NMDA receptor antagonists.

1. Cholinergic hypothesis:

According to the cholinergic hypothesis, memory impairment in patients with senile dementia of AD results from a deficit of cholinergic function. It was found from research that the loss of cholinergic innervations of the hippocampus and cerebral cortex couples with the loss of cholinergic neurons in the basal forebrain. Thus the treatment for AD has mainly been focused in the cholinergic hypothesis [13]. It includes

➢ **Acetylcholinesterase inhibitors**:

The enhancement of the central cholinergic function has been regarded as one of the most promising approaches for the treatment of AD by means of AchE inhibitors. They interact with peripheral active site of enzyme and acts as potential inhibitor for formation of amyloid [14-17]. Tacrine, which is an acridine derivative, was found to be a potent acetyl cholinesterase inhibitor. It is an orally active amine and readily enters CNS. It increases the release of Ach from cholinergic nerve endings. Additionally Tacrine may inhibit MAO (monoamine oxidase), decrease release of GABA and increase the release of noradrenaline, dopamine and 5-HT from nerve endings. It is useful in improving memory performance in AD patients [18]. Its derivatives such as velnacrine and surnacrine have also been reported as AchE inhibitors [19]. Unfortunately, Tacrine has shown side effects such as hepatotoxicity, abdominal cramps,

nausea, and vomiting. Physostigmine, a reversible AchE inhibitor has shown some efficacy in improving cognitive function in Alzheimer type of dementia [18]. But its use is limited as it has short half life, variable bioavailability and narrow therapeutic index. Heptyl physostigmine, a more lipophilic analogue is reported to be less toxic than physostigmine while retaining its in vitro AchE inhibiting potency. 8-carba physostigmine has greater potency and reduced toxicity as compared to physostigmine [20]. Donepezil possess the AchE inhibitory activity. Donepezil and rivastigmine have been marketed recently for the treatment of the cognitive symptoms of AD. [21, 22]

- **Acetylcholine release modulators:**

Acetylcholine release modulator, linopiridine enhances the potassium evoked Ach release from rat cortex, hippocampus and caudate nucleus in vitro [23]. Another mechanism of the stimulation of the Ach is via antagonists of H_3 histamine receptors (H_3-HRs). Two drugs namely clobenpropit (H_3-HR antagonist) and thioperamide (H_3-HR antagonist) have been reported for the treatment of AD [24, 25]. Stimulation of Ach release via the increase of the presynaptic uptake of endogenous choline, found due the AchE catalysed enzymatic degradation of Ach is considered to be an alternative to the receptor regulated Ach release [26].

2. Hormone replacement approach:

Estrogen enhances cerebral blood flow, prevents atrophy of cholinergic neurons, reduces oxidative stress, and modulates the effects of nerve growth factors. It may also reduce neuronal injury by decreasing formation of Ab [27]. Observational studies have shown estrogen-containing hormone therapy with reduced AD risk. However, in the Women's Initiative Memory Study (a randomized, placebo-controlled trial of women 65-79 years of age) on oral estrogen plus progestin doubled the rate of dementia; with heightened risk appearing soon after the treatment was initiated. Based on current evidence, hormone therapy is thus not indicated for the prevention of AD [28].

3. Anti-inflammatory approach:

Genetic evidence suggests that generation of amyloid ß peptide is the pivotal step in the pathophysiology of AD. The mechanism by which this peptide induces neurodegeneration may involve inflammatory processes. Pharmacological suppression of inflammation may therefore ameliorate the neuropathology. Basic research studies provide substantial evidence that inflammatory processes present in the brains of patients with AD are destructive, and that anti-inflammatory drugs can provide protection. Futhermore, epidemiological studies suggest that anti-inflammatory drugs reduce the risk of AD. However, there is not yet any strong evidence from completed randomized controlled trials that anti-inflammatory treatment is beneficial. Large trials of glucocorticoid therapy, hydroxycholoroquine, and non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of AD have so far been disappointing. Several studies including a large primary prevention trial with NSAIDs are still in progress. Major issues of selection of patients, drug regimen, and duration of treatment remain unresolved. Ibuprofen and Naproxen have been found to reduce the severity of AD. Rofecoxib is under clinical innvestigations in AD patients [29]. Numerous reports have indicated that patients suffering from inflammatory diseases (e.g., arthritis) who take anti-inflammatory medication have a reduced risk of developing AD. Thus, the first generation anti-inflammatory cyclooxygenase (COX) inhibitors such as aspirin and indomethacin have been tested as potential therapeutics in AD. Because

the inhibition of COX-1 is also known to cause tissue damage in the gastrointestinal system from the resultant reduced cytoprotection, selective COX-2 inhibitors are being investigated and tested clinically as potentially better therapeutics for AD patients. However, such drugs may also trigger unwanted effects for example the COX-2 inhibitors, which reduce the production of one type of eicosanoids, the porstaglandins, may increase the production of other eicosanoids; i.e., the leukotriene B4 (LTB4), which is one of the most potent endogenous chemotactic/inflammatory factors [30].

4. **Neurotropins**:

The infusion of nerve growth factor (NGF) into the adult rat brain was found to completely prevent the death of basal forebrain cholinergic neurons both spontaneously and after injury [31,32]. The Phase I human clinical trials were initiated in 2001 in eight AD patients. In the patients who received injection without complication, there were no adverse events observed over 2 years and no signs of non-targeted NGF spread [33].

5. **Agents that stimulate the neuropathic effects:**

Compunds namely propentofylline, citicoline and AIT-082 have a neuroprotective and cognition-stimulating activity via stimulation of neurotrophic function in CNS. Further development of propentofylline however was discounted after phase 3 clinical trial due to decrease in the level of radical oxygen species and cytokines, which results from suppressed activation of microglia in degenerative process [34]. Citicoline, an endogenous intermediate in the biosynthesis of structural membrane phospholipids and brain acetylcholine may improve memory via its neurotrophic effect [35, 36].

6. **Inhibition of amyloid formation and neurofibrillary tangles**:

The proteolysis of the membrane anchored amyloid precursor protein (APP) results in the generation of the β amyloid which is thought to be responsible for the pathology and subsequent cognitive decline in AD [37, 38]. The amyloid approaches postulate that agents that decrease β amyloid level in vivo would have promising therapeutic benefit in AD [39]. Amino acid derivatives, amine and urea analogues and hydroxyl-hexanamide derivates have been reported to inhibit β amyloid synthesis or/and its release [13].

Statins have been proven to decrease in vivo cerebral Aβ levels. Numerous early epidemiologic studies indicated that the use of statins significantly reduces the risk of AD However, recent large prospective cohort studies and two large randomized placebo-controlled trials of statins for coronary heart disease prevention failed to provide evidence of a protective effect against cognitive decline. The pattern of results obtained thus far suggests that statins may slow progression of the neurodegenerative process, but may not be able to reverse neuronal degeneration once it has occurred [27].

7. **Antioxidants:**

It was found that two daily doses of vitamin E (alpha tocopherol) or selegiline delays progression of AD. However, high doses of vitamin E can cause nausea and cramps and may increase the risk of bleeding in patients with coagulation abnormalities or people taking blood thinning drugs [40, 41].

8. **NMDA Receptor Antagonists:**

Excessive activation of NMDA receptors by glutamate increases the vulnerability of CNS neurons leading to neuronal degeneration. Memantine (trade name Namanda, Forest) blocks glutamate gated NMDA channels, thereby blocking pathological activation and preserving physiological activation [42, 43].

Memantine has been proved for the treatment of advanced stages of AD and is many times used in combination with donepezil for better outcomes [44].

CONCLUSION

There have been essentially three periods of Alzheimer's research. The first was the definition of the disease by clinicians and pathologists. The second was the neurochemical work, which led to the identification of the cholinergic lesion in the disease, and upon which most of the current therapies are based, and the third is the molecular biological and molecular genetic approach to the dissection of the pathogenesis. This third era of research undoubtedly holds the greatest promise in developing mechanism based therapies. However, it has to be acknowledged that no therapies for any neurologic or psychiatric disease have, as yet, been developed by this approach. Until then, treatments aimed towards blunting cognitive decline remain the standard of care.

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