A Pathophysiological and Pharmacological Review on Alzheimer's Disease: A Current Need

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Developing countries including India faces major setback in medicine and public health due to the neurodegenerative disorders. Among various neurodegenerative diseases like Parkinsonism, Hunting ton's disorder, Amyotrophic lateral syndrome, Alzheimer's is a usual subtype of dementia which has affected about 25 million people globally in 2000 and this statisticis believed to increase to 114 million in 2050. Aging has been found as one of the factors associated with Alzheimer's disease. Their association was confirmed with an increase in the incidence of this disease. A measure of the main constituent of plaque, cerebrospinal fluid levels of Aâ, and constituent of a neurofibrillary tangle, tau protein are the in-vivo biological markers of Alzheimer's disease patients. From ancient times various herbal plants were used for the treatment of Alzheimer's. The Pharmacological drugs used were Anticholinesterase, Muscarinic receptor agonist, Glutamate receptor antagonist. The newer monoclonal antibodies were introduced for the treatment but the success rate was merge. Resveratrol, an activator of silent information regulator type1(SIRT1) was the latest drug in treating this neurodegenerative disorder. The multifactorial aetiologies leading to neurodegeneration in Alzheimer's made the treatment more complex. At present, the introduction of novel therapy mainly targeting on the pathophysiology of neuroinflammation mediated by microglia and astrocytes gave a newer insight on Alzheimer's. The determination of biomarkers and newer detection techniques can help in the future for early detection in elderly patients and better pharmacotherapy in this complicated disease.

Keywords: Neurodegenerative disorder, Alzheimer's Disease, Monoclonal antibody, Anticholinesterase, tau proteins,Glutamate receptor antagonist.

Neurodegenerative disease, a consequence of progressive loss of structure or functions of neurons. Developing countries including India faces major setback in medicine and public health due to these neurodegenerative disorders. Among various neurodegenerative diseases like Parkinsonism, Hunting ton's disorder, Amyotrophic lateral syndrome, Alzheimer's is a usual subtype of dementia which has affected about 25 million people globally in 2000 these statistics are believed to increase to 114 million in 2050[1],[2]. Alzheimer's disease is due to the death of nerve cells in the cerebral cortex and the elderly people are the common population who is being affected by this fatal disease. The lack of awareness and understanding of these neurological diseases has made a huge impact on the lives of theses elderly people and also hindering their treatment. However, still there is a need for a disease-modifying agent that can quench the current scenario[3].

A brief history of Alzheimer's disease

Dr. Alois Alzheimer, a German neurologist was the one who identified the 'presenile dementia' and the disorder was coined by his name Alzheimer's disease. This psychiatrist and neuropathologist noticed the changes in the brain tissue of a 51year old woman, Auguste Deter which resulted in the symptoms of behavioral abnormalities and short-term memory loss. The pathological findings of Alzheimer's disease are senile plaques, clusters of beta-amyloid protein outside the cells, and tangles of tau protein inside the cell. A major transformation occurred after identifying the histopathological findings and several kinds of researches on dementia by Robert Katzman in 1976 has helped in determining the fourth cause of death in elderly people as Alzheimer's disease. The clinical finding in these patients is impairment of memory, disturbance in reasoning, planning, language, perception and this is also a major known cause for dementia.

Further research in the 1980s has given the latest yardstick for dementia and Alzheimer's for their clinical diagnosis[4,5]. Various studies carried during this period displayed that the episodic memory impairment as the initial and major clinical symptom in these patients. Other studies have revealed, visuospatial deficits as another clinical problem in Alzheimer's patients but to be considered as a less salient outcome when compared with cognitive deficits[6]. Later in the1990s and 2000, a mutation in genes was identified in studying Alzheimer's disease.

Aetiology of Alzheimer's Disease

The majority of Alzheimer's disease occurs on an irregular basis. Aging has been found as one of the factors associated with Alzheimer's disease. Their association was confirmed with an increase in the incidence of this disease[3]. With relation to age, they have been categorized into three groups. They are Early-onset, Intermediate, and Late on-set of disease. The age group in early on-set is around 40-60 years, in Intermediate group 60-80 years and the late-onset is after 85 years[7].

In the young age group, positive family history and mutation in dominant genes are the known primary risk factors. Mutation in three separate genes, amyloid precursor protein gene on chromosome 21, the presenile 1 gene on chromosome 14, and Presenile 2 gene on chromosome1 are the dominant genes responsible for early-onset of Alzheimer's disease[8,9]. This genetic mutation holds only 1-2% of cases falling under this category. A Head injury can also accelerate the appearance of these symptoms.

In intermediate onset, the prevailing genetic mutation was €4 Allele for apolipoprotein E, a low-density lipoprotein cholesterol carrier. The present gene mutation was responsible for 50-60% of cases regardless of their family history of dementia. Other risk factors are cardiovascular diseases, high blood pressure, diabetes mellitus, higher cholesterol, and high body mass index. In the late-onset, only the age is been associated as a risk factor for the onset of the disease[10].

Biomarkers of Alzheimer's Disease

The effect of the past twenty years of research has made an effect in spotting the in-vivo biological markers. A measure of the main constituent of plaque, cerebrospinal fluid levels of Aâ, and constituent of a neurofibrillary tangle, tau protein are the in-vivo biological markers due to their specified pathological changes in the brain of Alzheimer's disease patients. PET imaging to reveal the deposition of amyloid in the brain was done with an agent, Pittsburgh compound-B was developed by Klunk and colleagues. Recently, a tau binding agent was also developed which is in the review.

Neuroimaging measures of hippocampal, cortical, and brain atrophy was also used as a detector for neurodegenerative changes of Alzheimer's disease. The advanced methodologies are, state functional MRI and diffusion tensor imaging. Discoveries of these markers made it possible for detecting early-onset of cognitive symptoms and also to differentiate from Alzheimer's disease from dementia. Some studies over these biomarkers have made possible in developing various treatment strategies for Alzheimer's disease[11,12].

Herbal Treatment for Alzheimer's disease

The treatment of dementia dates back to the ancient Chinese treatment using single and a mixture of herbs. Ancient books such as "Complete Work on Jingyue" in 1624, records the first-ever of the herbal mode of therapy in dementia. Notable herbs like Huperzine A, Gingko biloba, Panax ginseng, Salvia officinalis, Ba Wei Di Huang Wan- an ancient mixture of Rehmannia powder mixed with seven plants, and then mixed with honey

& Yi-Gan San formula lypophilised dry extract with a mixture of seven different rootstock and its branches. The important objective in the treatment was to increase the cognitive status and improving repetitive- behavior in these patients[13].

Huperzine A

A naturally occurring alkaloid compound derived from firmossHuperzia serrata. The alkaloid-derived from the active medicinal plant is similar to caffeine and cocaine. The alkaloid compound is sold as a dietary- supplement which is been used worldwide for the treatment of memory loss and mental impairment. Various clinical trials performed in Chinese medicine proved the effect of Huperzine A in the memory loss.

Ginkgo biloba

This herbal medicine has been used for thousands of years in Chinese medicine. Ginkgo biloba extract is useful in the treatment of various ailments including in improving the symptoms and slowing the disease progression in Alzheimer's patients. Many studies performed earlier found Ginkgo biloba extract most effective in the early stages of Alzheimer's disease. The effectiveness was found by increasing cholinergic activity and by normalizing Ach receptors in the hippocampus of the brain. A standardized extract with 24% of Ginkgo flavone glycosides was found to be the effectual form of Ginkgo biloba extract.

Melissa officialis and Saliva officinalis

Reports from numerous studies have shown Mulissaofficialis improves cognitive functions and also helps in reducing agitation in mild and moderate Alzheimer's patients. Similar to Ginkgo biloba extract they also act on Ach receptors in the central nervous system. The efficacy of lemon balm was measured by using cognitive subscales of Alzheimer's disease Assessment Scale and the clinical dementia Rating -Sum of the boxes score[14,15].

Ayurvedic medicine was one of the world's oldest holistic healing system which was native to India and Indian subcontinent. The treatment in this medicinal system was a personalised treatment system where a delicate balance has to be maintained between mind, body, and spirit. In the United States, this medicinal system was considered to be a form of complementary and alternative medicine. The medicinal plants which were used for the treatment of Alzheimer's disease were Ashwagandha (Withaniasominifera), Tumeric (Curcuma longa), Brahni (Bacopa monnieri), Shamkhapuspi (Convolvulus pluricaulis), gotu kola (Centella asiatica), guggulu (Commiphoramukul) by increases the memory in these patients. These medicinal plants possess compounds like lignans, flavonoids, tannins, polyphenols, tripenes, sterols, and alkaloids with pharmacological- effect of anti-inflammatory, anti-amyloidogenic, anti-cholinesterase, hypolipidemic, and antioxidant.

Jyotishmati (Celastruspaniculatus)

This herb was used for treating brain-related disorders and to improve intellect. From this herb, oil form extracted from seed was used for improving memory.

Ashwagandha (Withaniasomnifera)

The Rasayana form of this plant was prescribed for improving health, longevity, arresting the aging process, revitalizing the body in debilitated condition, and increasing the immunity. Alkaloid extract was used as a calming effect of the central nervous system.

Jatamansi (Nardostachysjatamansi)

The root of this plant was used in powder form for the treatment of various neuropsychiatric illness.

Tumeric (Curcuma longa)

Various pharmacological actions like antioxidant, anti-inflammatory, antibacterial and anti-aging properties are present in turmeric. They also possess vitamins and minerals. The anti-inflammatory of this herb has been used for reducing the risk in Alzheimer's patients.

Guggulu

Guggulu, helpful in reducing cholesterol levels and inflammation. They have also been used for healing bone fracture, arthritis, gout, rheumatoid arthritis, atherosclerosis, obesity, and hyper-lipidaemia. The other factors influencing a dementia-like increase in cholesterol levels can be taken care of by using this herb due to its anti-cholesterol levels.

Brahmi (Bacopa monnieri)

This plant has produced an effect in various disorders like mental retardation, poor memory, epilepsy, insanity, anaemia, leprosy, renal and blood disease, and poisoning.

Shaukhpusphi (Convolvulus pluricautis)

This plant has a potential effect in treating nerve disorders, mental aberration, anxiety

neurosis, internal hemorrhage, spermatorrhoea, and other diseases[16].

Pharmacotherapy

Alzheimer's disease has become a major health hazard affecting mostly the old people above 60 years. Over past decades, the priority for treating these patients was mainly by targeting centrally acting anticholinesterase and to a lesser extent on Muscarinic agonist and acetylcholine releasing agents. With the known pathophysiology, the treatment was focussed on production, aggregation, and clearance of Aâ plague and also on neurofibrillary tangles.

Anticholinesterase

Tacrine, Donepezil, Rivastigmine, and Galantamine are the cholinesterase inhibitors used in the treatment of Alzheimer's by preventing the degradation of acetylcholine after their biosynthesis. In this category of drugs, tacrine was the first authorised anticholinesterase which was used in the Unites States for symptomatic treatment of Alzheimer's. This is an irreversible and non-competitive inhibitor of acetyl and butyryl-cholinesterase with its major action on the latter enzyme. Tacrine produced severe hepatotoxicity as its adverse effect which restricted its usage and also reduced its efficacy. Donepezil is a reversible inhibitor of acetylcholinesterase with a longer half-life and it is the anticholinesterase that is commonly prescribed in the United States and Europe. When compared with Tacrine, Donepezil lacks hepatotoxicity as an adverse effect but prone to cause nausea, vomiting, and diarrhoea. This drug produced its effect by directly enhancing central and peripheral cholinergic activity. Rivastigmine, a pseudo-irreversible inhibitor of acetyl and butryl cholinesterase with shorter half-life due to its metabolism by these enzymes. The higher dose of this drug showed a better therapeutic effect with an apparent central and peripheral side effect. Galantamine, a reversible and competitive inhibitor of acetylcholinesterase with mild action on butyrylcholinesterase. It is a clinically effective drug with gastrointestinal adverse effects.

Muscarinic Receptor Agonist

Milameline and Xanomeline are second-generation muscarinic receptor agonists which were developed with better pharmacokinetics when compared with first-generation drugs. Even with these advantages, these drugs were not able to be successful in treating Alzheimer's disease.

Glutamate Receptor Antagonist

Memantine, an NMDA antagonist has been used in Germany for the treatment of a moderate and severe type of Alzheimer's disease and also used in other types of dementia. The adverse effects were constipation, fatigue, headache, and confusion[17].

A Newer compound acting on recipient Aâ Proteins- Success or Failure

Verubecestat, a â- secretase1(BACE1) inhibitor was a newer drug acting on Aâ Proteins by involving the mechanism of inhibiting the proteolytic cleavage of amyloid precursor protein(APP). This drug was not successful due to its insufficient efficacy and risk/benefit ratio in Alzheimer's patients and therefore withdrawn from the Phase III clinical trial[18].Lanabecestat, another try which was also withdrawn from clinical trials due to its pre-judicious effect on Alzheimer's disease[19]. Simultaneously Atabecestat, a non-selective BACE1 was also discontinued from Phase II/III trials since it produced an unfavorable adverse effect of increasing liver enzymes during the trial[20]. The trial of Semagacestat was preceded without considering the results from an earlier trial and this drug was also withdrawn before finishing the Phase III trial. The reason for the withdrawal of this drug was the adverse effect like skin cancer and infections in the study population[21]

Tramiprostate, anti-glycosaminoglycan compound was targeting the inhibition of Aâ aggregation till the Phase II trial but this drug was also not beneficial for the cognition of Alzheimer's. The cognition was measured by using Alzheimer's Disease Assessment Scale-Cognitive Subscale. This drug was useful in stabilising Aâ42 monomers and thereby inhibiting the amyloid aggregation[22].

Monoclonal antibodies in Alzheimer's disease

Solanezumab, Bapineuzumab is Aâ humanised IgG1 monoclonal antibodies that can execute their effect on central epitopes of soluble Aâ monomers and N-terminus Aâ42. Recently, solanezumab was used in symptomatic and asymptomatic patients, prone to progress for Alzheimer's disease. Combination therapy of solanezumab and gentenerumab was tried but the combination failed, due to the lack of producing clinical benefit and combination with BACE1 inhibitor, an apparent adverse effect was produced.

The main objective behind the combination therapy was to increase immune response towards Aâ plaques and to improve the Aâ clearance and to inhibit the formation of new Aâ with BACE1 inhibitors. Aducanumab, was an Aâ-targeting monoclonal antibody and effective in a dose-dependent manner. This drug act by binding to Aâ soluble oligomers and insoluble fibrils and also reduces calcium dyshomeostasis in the infected neuron, since neuronal calcium in Alzheimer's brains is affected. Aducanumab failed to counteract the cognition deterioration in these patients, and therefore it was halted in Phase III clinical trial. BAN2401 is another humanised monoclonal antibody which produced a favorable therapeutic effect in Phase II clinal trial by showing 30% delay in cognitive impairment in mild-moderate Alzheimer's patient within 18 months and 47% delay for the high dose.

Passive immunization was one more feather to be added for pharmacotherapy in which exogenous monoclonal antibodies were administered to the patients. These monoclonal antibodies are highly potent in suppressing the aggregation of Aâ and disaggregating pre-existing Aâ fibrils. Even the higher dose of the monoclonal antibodies showed a safety profile[23].

Novel Approach to Alzheimer's

In the novel approach of Pharmacotherapy, the main objective was on pathophysiology and synergistically targeting several molecules. Inhibition of glycogen synthase kinase-Sâ(GSK-3â) and mammalian target of rapamycin(mTOR) benefits in decreasing neuroinflammation by increasing Aâ clearance and reducing tau phosphorylation. The mammalian target of rapamycin inhibition also activates the ubiquitin-proteasome system and autophagy.

Methylene blue, one of the antitau disease-modifying agent act on tau pathology through GSK-3â and tau aggregation. But the beneficial effect of methylene effect was not adequate due to its partial inhibition on tau aggregation.

Metformin, a type II antidiabetic drug exhibited anti-inflammatory and neuroprotective against cognitive deterioration in Alzheimer's disease. This antidiabetic drug improved the memory formation by hindering the neuronal apoptosis and promoting neurogenesis in the hippocampus by activation of AMP-activated protein kinase (AMPK)pathway.

Resveratrol, an activator of silent information regulator type1(SIRT1), a neuroprotective protein deacetylase can reduce tau acetylation and downregulate BACE1 by which they can increase degradation of tau and reduce Aâ production[24,25].

CONCLUSION

An elaborate review of Alzheimer's disease was a required research topic due to its increasing occurrence during the present era. The numerous studies carried during the past decades show major effects taken for developing new drugs for the treatment of Alzheimer's. But untiring research carried by various research scholars was not successful in accomplishing a better pharmacotherapy for this disorder. The multifactorial aetiologies leading to neurodegeneration in Alzheimer's made the treatment more complex. At present, the introduction of novel therapy mainly targeting on the pathophysiology of neuroinflammation mediated by microglia and astrocytes gave a newer insight on Alzheimer's. The determination of biomarkers and newer detection techniques can help in the future for early detection in elderly patients and better pharmacotherapy in this complicated disease.

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