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Alzheimer's disease: A Common Form of Neurodegeneration

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Mini Review

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INTRODUCTION

The human nervous system is an extremely complex structure, having billions of nerve cells or neurons [1]. Central nervous system (CNS) is a vital organ system [2-4]. Nerve cells of the central nervous system rarely divides after differentiation [5]. Neurodegeneration term refers to progressive loss of neurons. Alzheimer's (AD) and Parkinson's (PD) diseases are the most common neurodegenerative disorders in elders [6,7]. Progressive cell death in brain neuronal circuits occurs too often from brain injuries caused by diseases like Parkinson's disease and Alzheimer's disease [8]. Alois Alzheimer reported the autopsy findings of the brain of a woman who died of dementia at the age of 55 in 1906. He explained a "peculiar severe disease process of the cerebral cortex" with "miliary foci" (β-amyloid plaques) and "fibrils" (neurofibrillary tangles). The condition was termed as "Alzheimer's Disease" in 1910 in Kraepelin's textbook of psychiatry. Alzheimer's findings came into notice when the original histological slides were re-examined in 1998 using modern histochemical and genetic techniques [9,10]. Alzheimer's disease (AD) is one of the most devastating neurodegenerative disorders [11]. Age is the most important aspect determining the incidence and prevalence of neurodegeneration [12], cognitive impairment and dementia [9,13,14]. In a cohort study in USA the age specific rates of all-cause of dementia increases from 4·85 per 1,000 people in 65-69 year's age group to 84·19 per 1,000 people in 90+ year's age group [9,15]. Social isolation appears to increase cognitive decline irrespective of AD pathology, and the harmful effects of AD pathology are minimized by social engagement [9,16]. The prevalence of AD doubles every 5 years, after the age of 65 years. Furthermore the prevalence of AD in Late onset alzheimer's disease, in individuals over age 70, was found to be 2.3 million in 2002 .The prevalence of AD in patients of age 65 and above was 4.5 million in 2000 in U.S. The prevalence was latter updated to 5.3 million in 2008. The prevalence of AD in the world is estimated to be around 35.6 million in 2010.The number for the future are still exceeding with estimated 65 million in 2030 affected with AD and 115 million in 2050 affected with AD costing our global economy US$604 billion [17,18]. Perea RD, et al. suggested that individuals at early stages of Alzheimer's dementia did not appear to have significant white matter degeneration compared to non-demented elderly subjects [13,19,20]. AD is characterized by intracellular neurofibrillary tangles, intra-neuronal accumulation of hyper-phosphorylated tau forms and extracellular amyloid β-peptide (Aβ) deposits contributing to senile plaques [11,15,21]. Aβ is responsible for senile plaques (SPs) and tau is responsible for neurofibrillary tangles (NFTs). But, the primary cause for AD is the deposition of Aβ [22]. Aβ is a peptide which is a part of larger protein amyloid precursor protein (APP) [23] APP is a single-pass transmembrane protein with large extracellular domains. APP modulates cell growth, movement, neurite outgrowth, and cell survival [24,25]. The most important role of APP in the development of Alzheimer's disease depends on the toxicity of the Aβ peptide. Aβ fibrils are acutely toxic to neurons resulting in cell death due to its oxidative

effects [26-29]. Aβ generates the reactive oxygen species (ROS) which is responsible for neuron damage [30-34] as mutation of a single amino acid of the Aβ peptide eliminates its ability to generate ROS. Hugon J et al. reported that Aβ oligomers can lead to the production of TNFα [35,36] which causes memory impairment in mice and monkeys [37]. Soluble Aβ also controls the cleavage and phosphorylation of tau, both of which are important for neurofibrillary tangle (NFT) generation [25]. Neurofibrillary tangles composed of tau fibrils (NFTs) are an increasingly recognized part of the AD pathogenesis. Their intracellular formation around nerve endings signifies the extracellular accumulation of Aβ plaques. The fibrils of tau protein in AD brains are known as paired helical filament (PHFs) which is a structural form that tau proteins seem to aggregate in AD. Tau protein is surrounded by the Aβ protein in AD.[38-40]. Free radicals [41-43] are produced by the amyloid peptide once it is formed outside the neurons, and these free radicals were found to be neurotoxic to hippocampal cells and the synaptosomal membranes. These free radicals also damage the lipid membranes (lipid peroxidation) of the neurons leading to death [44-49]. Oxidative stress-inducing metal ions, such as iron (Fe), copper (Cu), zinc (Zn) and aluminum (Al) may contribute to the formation of SPs/NFTs and neuronal damage in the AD brain. Aluminium [50,51] is one of the major metal that cause free radical generation, giving Al phosphate injections into the brains of rabbits caused epilepsy and neurofibrillary changes [21,45,52]. Al is associated with the aggregation of Aβ and p-tau, and is also involved in Aβ deposition. So, due to free radical generating property of Al, it promotes cognitive impairment in rodents and humans [21,52]. Bastian et al. discussed the involvement of bacteria as a causal agent for the neurodegenerative diseases, and related the evidence to involvement of spiroplasma in the pathogenesis of the encephalopathy as a model for the neurodegenerative diseases (mainly AD) [53]. Gardener et al., discussed the role of diet in the developement of neurodegenerative diseases. Diet plays a major role in the development of neurodegenerative diseases such as Alzheimer's disease. There is increasing evidence that the components in the food that we consume, interacts with each other to impart disease protection and a higher level of health [54]. According to Cholinergic hypothesis, AD is caused by reduced synthesis of Acetylcholine (neurotransmitter)[55-57], in this the AchE (acetylcholine esterase) levels were increased which causes damage to the cholinergic neurons finally leading to cognitive impairments [12,58].

SYMPTOMS of AD

The most common symptom of AD is memory loss which worsens as the disease progresses. People with severe Alzheimer's cannot communicate and are completely dependent on others for their daily activities [6]. It is characterized by loss of cognitive [59] and non-cognitive functions. Non-cognitive symptoms occur just before the onset of cognitive symptoms. Non-cognitive symptoms in AD include behavioural and neurological symptoms. Cognitive function refers to an individual's perceptions, memory, thinking, social awareness and reasoning [17,60-62]. Cognitive decline includes multiple cognitive domains like decline in memory, orientation and executive functions. Depression and anxiety are common phenomena among patients with mild AD, whereas aggression, agitation, and apathy are more frequent in those patients at severe states of the disease [63]. Field T et al. described the smell and taste as an early marker of neurodegenerative diseases. The etiology and development of these sensory dysfunctions are not known, but the involvement dopamine [64,65], norepinephrine, serotonin, acetylcholine and orbitofrontal [66,67] cortex systems have been suggested in several of the neurodegenerative and neuropsychiatric conditions associated with smell dysfunction [68-70].

TREATMENT OPTIONS

The main problem in the treatment and management of AD is penetration in the blood brain barrier (BBB) [52,71]. Many research evidences suggest that various antioxidant therapies plays a major role in free radical scavenging and reduce oxidative stress, therefore they can be possible therapeutic options to treat AD [45,72,73]. Four major categories of drugs are used in AD treatment [74]:

- cholinergic treatment
- anti-glutamatergic treatment

- vitamins and anti-oxidants
- nonsteroidal anti-inflammatory drugs (NSAIDs)[75,76]

Out of these Acetylcholinesterase inhibitors (AChEIs) are the main line treatment options. AChEIs increases the availability of acetylcholine and thus facilitating cholinergic neurotransmission which in turn have positive benefits on cognition. Donepezil hydrochloride [77-81] is an acetylcholinesterase inhibitor, which improves cognitive function by inhibiting the enzyme acetylcholinesterase and activates cholinergic neurons via an increase of acetylcholine [82]. Blockade of glutamatergic neurotransmission by use of the uncompetitive N-methyl-D-aspartate (NMDA) antagonist (memantine) [83] subsequently blunts excitotoxicity, which is due to excess intracellular calcium, resulting in less generation of free radicals hence decreased neurodegeneration [74].

According to Bunik VI et al., transient improvement in cognitive function of patients with neurodegenerative diseases, including Alzheimer disease (AD) has been observed upon thiamin (vitamin B1) administration [84]. Thiamin acts as a coenzyme of the enzymes of central metabolism [85-88]. Many drugs are available for the treatment of Alzheimer's disease but, they only slow the neurodegenerative process and does not treat the disease [89], these usually treat the symptoms of the AD but cannot stop the progression of the disease. Also they have side effects such as dizziness, headache, constipation and confusion [82]. There is growing evidence on the effectiveness of non-pharmacological and psycho-social interventions, such as individualised or group-based reminiscence therapies, joint reminiscence sessions with family members, and stimulating sensorial experiences for adults with dementia that helps in delaying the progression of the disease [18,90]. Yellamma K et al. suggested that Sericin (silk protein) in a dose of 200 mg/kg body weight have neuroprotective properties as it reverse the memory impairments in AD-induced rat [12].

HOW AD is DIAGNOSED *IN VITRO*?

In vitro study is done by the researchers to find out the novel therapeutic agents that can treat AD. There are various parameters that are studied during the pharmacological studies. These are of two types: biochemical and behavioural parameters [12,38].

Biochemical Parameters

These include estimation of acetylcholine (ACh), superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GSH) [91-95].

Behavioural parameters

Various parameters are involved in the determination of AD in rats. These include:
Morris water maze test (Spacial learning)
Passive avoidance paradigm (Memory)
Locomotor activity by actophotometer
Stair case test (Spatial recognition) etc [12,96].
These parameters in all helps in determining the extent of action of novel drugs and thus, helps in development of newer therapeutic agent.

CURRENT SCENERIO

Recent researches are in a process of developing new drugs like Edaravone. Developed by the scientists from the University of South Australia, Edaravone can alleviate the progressive cognitive deficits of Alzheimer's disease [97,98]. Edaravone binds to the toxic amyloid peptide which is a major factor leading to degeneration of nerve cells and suppresses its action. Edaravone can suppress the toxic functions of amyloid beta to nerve cells-it is a free radical scavenger which suppresses oxidative stress that is a main cause of brain degeneration. The drug can halt the production of amyloid beta by inhibiting the amyloid beta production enzyme. It also inhibits the hyperphosphorylation of Tau protein, which can generate tangles accumulated in the brain cells and damage brain functions [99]. Secondly, a new drug

AZD05030, developed by Astra Zeneca tends to block damage initiated during the formation of amyloid-beta plaques which is a distinctive feature of AD. In the experiment cells under bombardment by beta amyloid plaques show restored synaptic connections and reduced inflammation, and the animal's memory, which was lost during the course of the disease, is restored [100].

CONCLUSION

AD is one of the major causes of dementia in the elders and is the most common form of dementia [59] that affects an estimated 33.9 million people worldwide. It is the sixth leading cause of death in the US [101]. Aging causes a slow but steady deterioration of the brain function leading to cognitive decline, memory loss, movement disorders and finally to functional decline and death [102]. There are many therapeutic agent present for the treatment of neurodegenerative disorders but they and not effective is completely curing the disease. These drugs usually slow down the rate of degenerative process but, in the end the damage will lead to fatal situations. In recent researches, scientist claim to have a potent drug for treating the neurodegeneration but, fails to slow or halt the disease progression. These drugs include mainly the flavonoid class and other free radical scavenging agents [103-106].

FUTURE DIRECTIONS

Researchers are on a verge of finding novel drugs for the treatment of AD. Current drugs help in masking the symptoms of Alzheimer's, but do not treat the underlying disease or delay its progression. Advancement may be the drug that would treat the underlying disease and stop or delay the cell damage that eventually halt the worsening of symptoms.

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