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Alzheimer's Disease and Memory Loss - A Review

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Abstract

Memory loss is one of the first symptoms in patients suffering from Alzheimer's disease (AD). During the course of the disease patients experience problems with their language, mood swings, and behavioural issues. Due to these conditions patients often withdraw from family or society with the fear and embarrassment and gradually, bodily functions are lost leading to death. The pattern of memory loss correlates with structural and functional integrity of brain. In patients with AD the formation of memory will be affected at molecular level disturbing the framework of neural networks.

Recently, many studies have focused on how the AD impacts episodic memory and the underlying neural processes. In this review the findings of these studies are discussed and the effects of current and promising treatments for AD on memory loss are summarized. The main aim of this review is creating awareness in understanding the intact and dysfunctional memory. Moreover the knowledge of a specific process of a particular memory loss due to AD helps the basic scientists in developing novel therapies and drugs.

Keywords: Memory loss; Alzheimer's disease; Dementia; Acetyl cholinesterase

Introduction

Memory is the ability of an organism to record, retain, and recall events, information and sensory stimuli, over a long or short. Lack or improper memory function can affect the quality of life and the ability to work efficiently. Alzheimer's disease (AD) has become a synonym for memory loss as it is the most common cause of dementia. Currently, worldwide almost 50 million people suffer from Alzheimer's dementia and memory loss related diseases and the World Health organization projected this number may even triple over the next 20 years [1-10]. The incidence of Alzheimer dementia increases with an increase in age making it a very common disease in aged person of more than 70. Due to advancements in the medical and biomedical field the longevity of life increased and this made the old aged people to live with Dementia of AD compulsorily [11-15].

Researchers have found six cognitive domains in patients suffering from AD. They are attention and affect, executive functioning, language, memory, visuospatial functioning, and memory impairment is the central problem in the patients. Actually AD is a polygenetic brain disorder which is neurodegenerative in nature and causes neocortical atrophy which develops over decades [16-18].

Opportunities for studying the preclinical stage of Alzheimer's dementia before diagnosis come rarely. The best way to study dementia in AD is to study persons who are at risk of dementia with high probability. There are is no effective treatments or medicines for AD induced dementia. But progression of the symptomatic development could be prevented and this could be best strategy to mitigate the condition.

Neuropathology of Alzheimer's

The amyloid deposits called as senile plaques are neuro pathological hallmarks which indicate atrophy process and neurofibrillary tangles in brains of AD patients. Neurofibrillary tangles are hyper phosphorylated tau protein in neurons, whereas senile plaques are amyloid-P species deposited in the extracellular space. Poorly myelinated in neurons of hippocampus, brains cortex which are related to memory and learning are the first signs of AD. Highly myelinated neurons will be affected only in the final phase of AD. Low myelinisation weakens the neurons as it increases the energy expenditure of neurons in nerve transmission. Parietal lobes, and some areas of the prefrontal lobe, are the last areas to mylenate in human brain increasing their vulnerability to AD [19-25]. Down regulation of synaptic genes in multiple regions of brain, synaptic stress or decay in brain or the cerebrospinal fluid (CSF) and changes in the molecular structure of can be seen in brain resonance spectroscopic studies of AD patients.

Causes of Alzheimer's Disease

Amyloid β-peptide (Aβ)

Many evidences, suggest that AD is triggered by neurotoxic 42-aa amyloid β-peptide (Aβ) assembly in the brain. $A\beta_{1-42}$ is derived by proteolytic cleavage of its precursor protein amyloid precursor protein (APP). Scientists proved that mutations in APP gene can cause familial AD and increases the accumulation of $A\beta_{1-42}$. $A\beta_{1-42}$ has the capability of self-association and forms into large, insoluble amyloid fibrils which can be found in AD neuritic plaques. This hypothesis of amyloid cascade was formulated in 1992, which proposed that the primary molecular pathogens of AD are these insoluble amyloid fibrils. But this hypothesis wasn't accepted. The amyloid cascade hypothesis was rectified by including pathogenic Aβ assemblies, but their structure differs entirely with amyloid fibrils. These assemblies will not be detected by normal assays like that of fibril deposits. Soluble oligomers have been considered to be the culprits for physical degeneration of synapses and in age-onset memory failure [26-30].

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Mitochondrial dysfunction

Aβ is considered as a potent mitochondrial poison affecting the synaptic pool [31] In Alzheimer's patients exposure to Aβ will inhibit many mitochondrial enzymes like Cytochrome C in the brain [32,33]. The accumulation of Aβ in damaged mitochondria of AD in the brains of AD patients intra neuronally can be found [34,35].

ApoE4

In late-onset AD still many unidentified genes are involved, each contributing a minor fraction of disease overall risk, which is an example of antagonistic pleiotropy. Recently, several studies have identified new genes and molecules involved in the onset of dementia in AD. Apolipoprotein is one of the best characterized genetic risk factor in late-onset of AD. Individuals with E4 (ApoE4) genotype or with ApoE4 carriers will have 4-10 fold increased probability of developing AD. Adaption of humans with diet of meat can also be a reason for the selection of ApoE3 for the AD in the evolutionary perspective. The progression of AD is not understood clearly till now [36-43].

Cell-cycle re-entry

Many scientists hypothesized that the failure in the normal suppression of cell cycle as one of the reasons for the onset of Alzheimer's disease [44]. Bio-markers of cell-cycle reentry especially in G1–S-phase boundary can be detected in all stages of AD and even in mild cognitive impairment [45,46]

Calpain-cathepsin hypothesis

Autophagic vacuoles or granulo-vacuolar degenerations can be seen in degenerating neurons of AD patients. This probably is a causative connection between neuronal death and autophagy failure. Hence, many scientists proposed that an age-dependent oxidative stress affects autophagic-lysosomal system through cleavage and carbonylation of heat-shock protein 70.1 (Hsp70.1). Membrane lipids are vulnerable to the oxidative stresses and they generate toxic peroxidation products that can carbonylate Hsp70.1. Many evidences suggest that Hsp70.1 is a molecular chaperone which repairs damaged proteins and maintains lysosomal integrity.

Impairments of lysosomal functions and stabilization is found to be driven by calpain-mediated cleavage of carbonylated Hsp70.1, which results in lysosomal permeabilization or rupture releasing the cell degradation enzymes, cathepsins which eventually lead to the AD. This hypothesis is called as calpain-cathepsin hypothesis, which is recently put forward by the scientists and currently most acceptable.

Synaptic failure

Many researchers concluded that the Alzheimer's disease may be disorder of synaptic failure [45]. It is evident that Hippocampal synapses declines even in patients with mild cognitive impairment [46].

Diagnosis of Alzheimer's Disease

The diagnosis is made on the basis of medical history from the relatives and behavioural, neurological and neuropsychological observations. Magnetic resonance imaging (MRI), Computer Tomography (CT), Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) which can be used in the determining cerebral pathology in AD patients. CCSVI has been evaluated using ECD, UDC, UDS, TCCS, and even MRI. Intellectual quotient can be assessed by memory testing. Application of Echo-color-Doppler technique to detect neuro degeneration can be used to find AD in patients [47-58].

Alzheimer's Disease Management

There is no prescribed method or form for AD prevention as the Research findings for treating AD have been highly inconsistent. Epidemiological factors of AD were associated with diet habits, cardiovascular diseases, and intellectual activities [59-63].

Presently, AD medications targets only secondary risk factors such as hypercholesterolemia, hypertension, smoking etc. Very few Drugs have shown little success to arrest the progression of AD. Hormone replacement therapy has also been proposed for treating AD but the research suggested that it still increases dementia. Change in lifestyle of AD patients including is recommended as a possible management strategy for AD. Some research findings suggested that Red wine, Caffeine, tea, cocoa, Vitamin A, C, E, Folic acid and minerals such as selenium and Zinc etc., were effective against AD management [64-70].

Some Studies have shown that the levels of Acetyl Cholinesterase (ACh) play an important role in the cognitive function. Recent medication strategies of medication for AD targeted the cholinergic activity improvement in the brain. Therefore, uses of acetyl cholinesterase inhibitors have been reported to improve clinical symptoms of AD. Conventional ACh inhibitors like donepezil, Galantamine, rivastigmine, tacrine, etc., are few examples [71-76].

Herbs in Treating Alzheimer's Disease

Gingko biloba contain bioactive compounds which promote blood flow in the brain [77-82] which enhances the neurotransmitters keeping the cerebral complex healthy. Currently application of *Gingko biloba* is done in combination with approved cholinesterase inhibitors despite side effects in using *Gingko biloba* [83-91].

Lycopodium serratum produces huperzine A, a potential therapeutic agent for treating AD. Huperzine A protects from neuronal apoptosis, Aβ-induced oxidative injury, Aβ mediated oxidative stress, and mitochondrial dysfunction, and reduces glutamate-induced toxicity which helps in clinical improvements of patients with AD [92-97]. It also reduces toxicity in the neurons by modulation of interaction between glutamate-NMDA receptors. Some other herbs like *Curcuma longa*, Periwinkle are also being used in treatment for AD [98-100].

Hypericum extract contains flavonoids such as quercitrin and quercetin show potential free radical scavenging activity, antioxidant activity through the inhibition of lipid peroxidation. Hypericum extract in combination with scopolamine has been proved to show antidepressant activity with memory-enhancing capability which can be used in treating AD. *P. tenuifolia* a traditional Chinese medicinal herb is used as tranquillizer for treating and preventing dementia in combination with scopolamine this herb is potential in treating AD.

C. paniculatus (Celastraceae) an Indian medicinal plant mainly used in the traditional Ayurvedic system for stimulating nerves, and as a diuretic, rejuvenant, tranquilizer etc., needs to explored for its potential in treating AD. Herbs like Ginseng, *M. officinalis* (lemon balm), *Salvia officinalis*, *Lavandula officinalis*, *Zizyphus jujube*, *Lepidium meyenii*, *Prunella vulgaris*, Curcumin, etc., were also proved to be having potential therapeutic effect on AD.

Conclusion

The number of AD patients is increasing every day. Unfortunately this disease has not known potential treatment methodologies or drugs. Intensive research and new interventions using latest monitoring and diagnostic tools for AD are required to cure the disease progression.

Herbs are promising in AD treatment which is another dimension needed to be focused. Many of the traditional herbs which have potent antioxidant and neuro protective effects needs to be further studied to identify novel therapeutic bioactive compounds for the treatment of AD.

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