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Review Article

Alzheimer's Disease: Stages and Treatments

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Abstract

Neurodegenerative disorders have been considered to play a primary role in alteration of normal physiology of patients worldwide. Alzheimer's disease (AD) represents a ravage disease which has currently enhanced the incidence rate of panoramic implications for uprising the health care costs. AD is characterized by irreversible and progressive loss of neurons from specific areas of the brain alongwith dysfunctional biochemical processes, ultimately leading to neuronal death. There have been a number of pharmaceutical therapies which are reported to show beneficial effects in AD which includes cholinesterase inhibitors, antihypertensives, insulin, secretase inhibitors, and herbal supplements. The objective of this review article is to represent the current therapeutic approaches employed in AD.

1.0 Introduction

Alzheimer's disease (AD), characterized by memory loss and cognitive decline, has been regarded as continuous in onset but relentless in progression. AD has been delineated firstly by a German psychiatrist and neuropathologist, Alois Alzheimer, in the year 1906.[1] The first clinical character arising in AD has been the impairment of short-term memory loss, whereas, awaken of distant memories has been preserved during the course of disease. Also, AD was previously known as pre-senile dementia, which has been a major health burden globally, which mainly affects the patients over 60 years.[2] Surprisingly, studies have documented that by the year 2050, 1 in 25 people will be affected by AD.[3-5] In advanced stage of AD, the additional cognitive abilities have been noted to get impaired. Moreover, the awakening and alertness of the patient gets unaffected before the stage reaches advanced.[6-7] However, the exact cause of AD are still unknown, but it has been documented to nearby reflect the accumulation of neurofibrillary tangles and reduction of acetylcholine in the cerebral cortex.[8-9] Various hypothesis have been suggested for the pathophysiology of AD, which include, cholinergic hypothesis; β-amyloid hypothesis; and tau hypothesis. Moreover, there have been various interventions in order to treat the patients present with them which include Angiotensin converting enzyme (ACE) inhibitors, cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) antagonist and insulin.[5-9] The present review article has been designed to describe the pathophysiology and treatment strategies for AD patients.

2.0 Symptoms of AD

Various symptoms of AD have been reported globally, which include gradual loss of memory in order to remember or store the information. In addition, a number of other signs and symptoms have been suggested like memory loss disrupting daily life style, challenges in planning and solving the easiest tasks, confusion with time and places, problems in communicating with others, diminished and poor skill in judgments, variations in mood and personality, and withdrawal from social activities.[10] However, AD has been documented to progress with time, followed by loss of cognitive and functional activities such as bathing, walking, dressing, eating and using bathroom.

3.0 Causes and Complications of AD

In the case of AD, various causative factors have not been known accurately. However, various hypothesis behind the pathophysiology of AD have been discussed, which include various causes and complication such as cholinergic hypothesis; β-amyloid hypothesis and tau hypothesis.[8-9] The cholinergic hypothesis state that the deficiencies of acetylcholine have been responsible for developing the symptoms of AD.[11] In the direct analysis, neurotransmitter in cerebral cortex showed a reduction of many substances, causing neuronal loss. Moreover, the cholinergic effect has been known to initiate the aggregation of β-amyloid, resulting in neuroinflammation.[12-13] Further, according to β-Amyloid Hypothesis, β-amyloid acts as a fragment of a larger proteins, referred to as amyloid-precursor protein (APP), that has been shown to penetrate through neuron's membrane.[14-15] Moreover, it has been reported that the aggregation of β-amyloid acts as a constant factor of AD. In AD, APP gets divided into various small fragments which tend to give fibrils of β-amyloid forming clumps, adhere outer surface of neurons, resulting in senile plaques.[6,16-19] According to tau hypothesis, the abnormal functioning of tau protein has been considered responsible in order to initiate the disease. In AD, abnormal accumulation of tau proteins has been suggested to occur.[20] The tau protein has been known to stabilize the microtubule, which are responsible for providing the nutrient and other molecules from all to end of axon when phosphorylated.[21] In AD, some changes in chemical behavior of tau results in the formation of neurofibrillary tangles inside nerve cell.[22] Furthermore, the microtubule disintegrates and finally tends to collapse the neuron's transport system, causing the death of the nerve cells.[23-24]

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4.0 Stages of AD

Epidemiologically, it has been well accepted that AD includes the gradual cognitive disabilities in the patients. However, various stages of AD have been suggested which include Alzheimer disease Stage I, in which the frequent memory loss of recent events occurs along with co-ordination problems such as writing and using objects, ultimately showing depression and apathy; Alzheimer disease Stage II, in which persistent memory loss occurs like forgetting the personal history and disabling to recognize the friends and family members; Alzheimer disease Stage III, in which the patient gets confused about past and present alongwith loss of ability to stable the mind, conversation extreme problems with mood and behavior.[7,25] Apart from the stages discussed earlier, another classification of stages of AD has been suggested which can be classified on the basis of diagnosis like Nill Impairment in which normal memory and cognitive abilities have been shown; Minimal Impairment/Normal amnesia, in which patient experiences the memory blunder and changes in thinking style identified by colleagues, family or physician; Mild Cognitive Impairment in which the patient has been known to experience difficulties with planning the things, and forgetting recent learnings; Mild Alzheimer, in which the patient is unable to handle the finances due to mathematical problems, forgetting the recent conversations, unable to carry out sequential tasks such as driving, cooking and shopping.[7,20] Additionally, other staged of AD includes Being Early Dementia/Moderate AD, in which the patient gets unable to recall personal history and independent to manage the information regarding society; Being Middle dementia/Moderate Severe AD, in which the patient shows complete loss of awareness of present events and unable to remember the things of past; and Severe Dementia, in which the patient has been suggested to require the assistance for making the events of daily living tasks.[7,20,25]

5.0 Pathophysiology of AD

Various pathophysiological mechanisms have been proposed for the pathogenesis of AD causing the cell death, resulted from many factors. However, exact pathology behind AD has not been clearly understood, but alteration in the production and accumulation of β-amyloid, the central phenomenon to degenerate the neuron, has been reported.[7] It has been suggested that AD involves the loss of neurons and synapses in cerebral cortex, which is supported by the fact that atrophy of affected regions like temporal lobe, parietal lobe and some parts of frontal cortex have been noted. The accumulation of aggregated amyloid fibrils, the torcin form of the protein, has been shown to cause destruction in calcium ion homeostasis of cell, which is responsible for programmed cell death.[25] In addition, the advanced stage of AD involves the multiple occurrence of senile plaques and neurofibrilary tangles, which are more abundant in the hippocampus and nearby regions of cortex.[26] Moreover, another possible factors have been discussed for the cause of cell death in AD, which involve the chemical changes in tau protein in microtubules. In addition, reacting oxygen species have also been suggested to be responsible for cell death by the initiation of chain reaction, resulting in the damage of cell membrane, mitochondria, protein and lipids. Further, as the cell membrane damage continues; various chemicals, toxins, and trauma produce inflammation; ultimately leading to the development of AD.[27-28] Furthermore, the level of N-Acetyl – Aspartate (NAA) has been suggested to cause abnormal physiology of neuron, ultimately leading to the progression and development of AD. Also, many inflammatory phenomenon and cytokines has also been documented to play an impulsive role in pathology of AD.[30-32]

6.0 Treatment of AD

Alzheimer's has been documented as a terminal disease, which has no cure ending on patient's death. However, various medications have been suggested in order to treat the symptoms, and progression of the disease. There have been a number of pharmaceutical therapies which are reported to show beneficial effects in AD which includes cholinesterase inhibitors, antihypertensives, insulin, secretase inhibitors, and herbal supplements.[33] The cholinesterase inhibitors have been known to enhance the neurotransmitters level in brain by stimulating the reduced activity of cholinergic neurons in AD, the mechanism being attributed to the presence of chemical entity that inhibits the cholinesterase enzyme from breakdown of neurotransmitter acetylcholine (Ach), resulting in enhancement of neurotransmitter acetylcholine.[33-34] In support, various epidemiological studies have reported that cholinesterase inhibitors slowed the worsening of signs and symptoms of AD, for example donepezil; galantamine; and rivastigmine. Moreover, memantine, a non-competitive NMDA receptor antagonist, has been used to treat moderate to severe stages of AD, by blocking NMDA receptors and inhibiting their overstimulation by glutamate, protects the brain cells from damage caused by glutamate.[33-37] In addition, studies have demonstrated that memantine is used to treat moderate to severe stages of AD when combined with cholinesterase inhibitors. Further, insulin has been reported to play an important role in the regulation of normal cell functioning. Several cognitive measures in patients with early AD has been improved by nasal administration of insulin.[38] The secretase inhibitors have also been suggested to show beneficial effects in the patients presented with AD by a mechanism involving in the inhibition of breakdown of APP in cell membrane into β-amyloid fragments.[39] In addition, many herbal supplements like ginkgo biloba, and withania somnifera have shown improvement in AD patients by their potent antioxidant and anti-inflammatory properties.[40-42] Furthermore, ACE inhibitors have been reported to penetrate the blood brain barrier (BBB), causing the reduction in the inflammation, and improving the signs and symptoms in the patients presented with AD.[43]

7.0 Conclusion

AD represents a complex disease affecting people worldwide that can be well defined as a disease which is continuous in onset but relentless in progression. Crucial care has been required in order to treat the patients by maintaining the daily lifestyle. A number of potential therapies have been suggested for the treatment of AD, but other novel targets are still to be investigated in order to completely treat and prevent the patients presented with AD.

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