Vol. 2 Issue No.4, October-December 2020 e-ISSN 2456-7701
Journal of Science and Technological Researches
A Peer Reviewed Journal
Origin of Innovation
Domain: www.jstr.org.in, Email: editor@jstr.org.in

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Date of Received	**18 October, 2020**
Date of Revised	**23 November, 2020**
Date of Acceptance	**06 December, 2020**
Date of Publication	**31 December, 2020**

https://doi.org/10.51514/JSTR.2.4.2020.19-24

To link to this article: http://jstr.org.in/downloads/pub/v2/i4/4.pdf

e-ISSN 2456-7701
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ABSTRACT

Background: Alzheimer's disease (AD) is neurodegenerative, progressive brain disorder and most common form of dementia. Dementia is a clinical condition characterized by progressive deterioration in cognitive domains, including memory, language, executive and visuospatial function, personality and behavior. Comprehensive search reveals that people with Alzheimer seem like they have lost their memory, challenges in planning or solving problems, gradually loss of capability to achieve normal task, puzzling day from night, loss of visualization and coordination, inappropriate use of words, inability to recognize and use familiar objects, mood change. Etiology of Alzheimer represent involvement of environmental factors, role of genes, social stressors, like discrimination or economic hardship, oxidative stress, mitochondrial impairment, neuro-inflammation, synaptic dysfunction, blood-brain barrier disruption, nutritional deficiencies, down's syndrome, head injuries, cardiovascular disease (high blood pressure, high cholesterol), lifestyle factors (lack of exercise, poor-quality sleep and a diet lacking fruit and vegetables), as well as metabolic conditions such as diabetes and obesity also plays role in building Alzheimer, while pathophysiology represents dysfunctional neurotransmission of acetylcholine, stress-associated signaling cascades (Gabanergic, glutamatergic, singling cascades) and abnormal extracellular accumulation of ß-amyloid plaque deposition and neurofibrillary tangles (NFTs) of hyperphosphorylated tau. Pharmacological agents are utilize in the management of Alzheimer and are proved to be effective in the controlling of dementia disorders.
Objective: Objective of this review paper is based on the study about pathophysiology and pharmacotherapy of Alzheimer's disease.
Methods: Several pathophysiological hypothesis of Alzheimer's disease were identified through searching relevant databases together with PubMed, Scopus, and Web of Science up to the year 2020, using the keywords Alzheimer's disease, symptoms, etiology, pathophysiology, diagnosis, pharmacotherapy.
Result: Alterations of ß-amyloid plaque deposition and NFTs of hyperphosphorylated tau were compiled in this article for easy learning of Alzheimer's disease.
Conclusion: Alzheimer's disease is a major illness/complex progressive neurodegenerative disorder, dementia or memory loss. This article targets to deliver a brief indication of neurotransmitter role as well as other pathophysiological variations in Alzheimer's disease. Animal models and specific biomarkers will help to identify and develop novel therapeutic agents with fewer side effects.

Keywords: *Alzheimer's disease, symptoms, etiology, pathophysiology, diagnosis, pharmacotherapy.*

INTRODUCTION

AD is one of the most important distressing, medical and social problems in older people in industrialized and non-industrialized nations. AD is a neurodegenerative and prominent protein-conformational disease (PCD) caused by the abnormal processing and polymerization of normally soluble protein [1-3]. Although there is increasing evidence that AD pathology starts depositing in the brain in midlife, the first medical indications usually occur after the age of 65 [4]. AD is a significant public health problem secondary to the increased life expectancy of the general population and a better appreciation of the socioeconomic consequences of the disease. It was defined by Alois Alzheimer in 1906 using criteria of progressive memory loss, disorientation, and pathological markers (senile plaques and NFTs) [5-7]. Although, primarily it was assumed that AD was a rare condition, and later it was considered to be an unavoidable consequence of aging. It is characterized clinically by progressive memory and orientation loss and other cognitive deficits, including impaired judgment and decision making, apraxia and language disturbances. These are typically accompanied by various neuropsychiatric symptoms (i.e. depression, apathy, anxiety, agitation, delusions, hallucinations) [8-9].

Etiology and pathogenesis

Risk factors for AD include age, family history, apolipoprotein E ε4 genotype, diabetes, hypertension, obesity, hypercholesterolemia, traumatic brain injury,

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e-ISSN 2456-7701
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and low education level. The main function recognized for tau is promoting microtubule polymerization and stabilization. Microtubules form part of the cytoskeletal framework in all eukaryotes and are composed mainly of heterodimers of - and - tubulin forming tubular polymers. Microtubules play a major role in cytoskeletal maintenance and act as highways for intracellular transport of organelles, vesicles, proteins, and signaling molecules.

Amyloid plaques

The main neuropathological features of AD appear to be senile plaques (SPs) and NFTs. The SPs seem to develop first in brain areas associated with cognition, and spread to other cortical areas as the disease progresses. The SPs consist, among other components, of insoluble deposits of amyloid p-peptide (Aß), a portion of the amyloid precursor protein (APP). Aß peptide is generated from APP by two consecutive cleavage events: proteolytic activity by ß-secretase generates one end of the Ap peptide, while? -secretase generates the other end, also by proteolysis. There appear to be two types of Aß: a longer species, Aß42, and a shorter species, Aß40. Aß42 seems to be deposited initially and may have a role in initiating the events that ultimately lead to amyloid deposition. It is still not clear if the SPs are the cause or a by-product of AD, although there are increasing data that dysfunction in the metabolism of APP with subsequent increase in the insoluble Aß is responsible for AD. Aß seems toxic to the neuron either directly, or indirectly by causing inflammation or increasing the production of free radicals [10-12]. The accumulation of NFTs in neurons is a second distinguishing feature of AD. NFTs are mostly formed by chemically altered (abnormally folded and phosphorylaled) tau protein, a protein involved in microtubule formation. Tangle formation is related to the severity of disease; the more advanced the stage of disease, the more tau tangles in the brain. Despite the presence of NFTs in AD, no cases of AD secondary to mutations in the tau gene on chromosome 174 have been reported, although frontotemporal dementias with Parkinsonism were found in some families with that mutation. The finding that the tau alteration follows Aß accumulation in AD affecting people is supported by recent data [6]. Tau proteins in AD are hyper-phosphorylated and abnormally folded compared to unassembled normal tau, and they have lost their normal abilities to bind and stabilize microtubules in the axon [13]. This loss of tau purpose is coupled with increased aggregation properties for the abnormal tau. Both a loss of normal function and a toxic gain of function are postulated, whereby paired helical filaments are able to co-aggregate with normal tau proteins [7, 14]. Epigenetics exploring neural syndromes and deals with the study of interactions between genes, expression of genotypes has developed fairly well and been widely studied in central nervous system-associated diseases comprising learning, motor, behavior, and cognition pathologies and disorders, [15-17]. this is also affect the environment or paternal genes, nutritional habits, trauma, stress or learning disabilities, exposure to chemicals or drug addiction on deoxyribonucleic acid and resultant structural disturbances, mutations, or changes [18-19]. The involvement of epigenetics has recently been explored in one of the major complex aging-related neurological diseases - AD. The onset of AD and its progress involves a complex interplay of various factors like aging, genetic mutations, metabolic and nutritional disorders, effect of and exposure to environmental variables, and most importantly the involvement of social factors [20].

Oxidative Stress (ROS)

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, such as superoxide anion, hydroperoxyl radical, hydrogen peroxide, and hydroxyl radical. Under normal conditions, cells permanently produce limited amounts of ROS by multiple biochemical processes. The “professional” ROS producers, such as mitochondria, peroxisomes, and endoplasmic reticulum, are the major sources. [21-23]. In mitochondria, ROS are produced permanently as a byproduct of ATP production by the electron transport chain. It is well documented that increased in ROS levels are highly toxic to cells, in which they damage essential macromolecules, such as DNA, RNA, proteins, and membrane lipids. Cells have developed several strategies to manage ROS.

In particular, they synthesize several enzymes that display antioxidant properties. Among this large family of antioxidant proteins are catalase, glutathione peroxidase (GPx), and superoxide dismutase (SOD), which protect against the damaging effects ROS [24-

e-ISSN 2456-7701
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27]. In addition, it has reported that microglial cells produce ROS, either in an attempt to eliminate pathogens or during the first steps of neuro-inflammatory processes. Several recent studies have established a direct, albeit complex relationship between neurodegenerative diseases of the AD/tauopathy types and microglial activation 28-30].

Diagnosis

According to the Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision, AD requires the following: new onset memory impairment; (2) another cognitive disturbance, such as aphasia, apraxia, agnosia, or executive functioning; and (3) a gradual, progressive course that results in significant functional impairment.

- **Fluorodeoxyglucose-positron emission tomography (PET),** scans show areas of the brain region in which nutrients are poorly metabolized. Identifying patterns of degeneration; areas of low metabolism: can help distinguish between AD and other types of dementia.
- **Amyloid PET imaging** can measure the burden of amyloid deposits in the brain. This imaging is primarily used in research but may be used if a person has unusual or very early onset of dementia symptoms.
- **Tau PET imaging,** which measures the burden of NFTs in the brain, is only used in research.

Management of Alzheimer's disease

The hypothesis that anti-inflammatory therapy can slow down the development of AD has gained support from some retrospective epidemiologic studies [31-33]. There are very few prospective double-blind clinical trials of nonsteroidal anti-inflammatory drugs (NSAIDS) in AD. Non-randomized studies with NSAIDS (indomethacin, ibuprofen, diclofenac, naproxen), steroids (low-dose prednisone [34-36] and other anti-inflammatory agents (hydroxychloroquine, colchicine) indicated favorable results in modulating the course of the disease. Unfortunately, these studies included small sample sizes. Recent studies have not replicated the previous positive results. However, at high-dose prednisone studies showed improvement, the use of high-dose steroids over a long period of time can cause substantial health problems. Another class of anti-inflammatory agents is that of the cyclooxygenase-2 inhibitors (celecoxib, rofecoxib). By being more specific for the brain than the currently available NSAIDs, they are now favored in clinical trial use for patients with AD. A major double blind placebo-controlled trial comparing rofecoxib with naproxen and placebo has now been completed and the results were negative [37-39].

Acetylcholinesterase Inhibitors (AChEIs)

There are two classes of medications which were reported for AD: the AChEIs and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. Treatment with AChEIs should be considered in patients with mild to moderate AD per the American Acdeny of Neurology practice guidelines for dementia. Three agents such as donepezil, rivastigmine, and galantamine are currently approved and marketed in the United States [40]. All three have been shown to be effective in double-blind placebo-controlled trials, showing some benefit on cognitive measures including memory and concentration as well as global and functional outcome measures; however, their therapeutic cognitive and functional effects seem to be modest in size and purely symptomatic [41].

Glutamate Receptor Modulators

Memantine is a glutamate receptor modulators and showing low to moderate affinity NMDA receptor antagonist that is used as an add-on to ongoing AChEI therapy. A recent meta-analysis of nine trials with a combined sample size of 2433 revealed that memantine had a valuable result on cognition, behavior, activities of daily living, and global function [42]. In contrast, Canadian Consensus guidelines on dementia from 2013 state that, while combination therapy of a cholinesterase inhibitor and memantine is rational and appears to be safe, there is insufficient evidence to support or refute use of memantine in moderate to severe AD [43].

Serotonin reuptake inhibitors (SSRIs)

SSRIs (fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine) are largely considered to be among the most efficient antidepressants to treat comorbid depression in AD dementia [44]. Mirtazapine, venlafaxine and duloxetine, which are combined selective noradrenalin and serotonin inhibitors, and bupropion are other widely used antidepressants in this population. There is evidence from meta-analyses that some atypical antipsychotic

e-ISSN 2456-7701
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drugs, specifically risperidone and aripiprazole, confer benefit in the treatment of aggression in people with Alzheimer's disease over a period of up to 12 weeks [45]. Benzodiazepines also shows their effect to reduce agitation and anxiety. Taking Benzodiazepines for long time, showed some adverse events like rapid cognitive and functional decline in older people [44].

Anticonvulsant drugs like carvamazepine can also reduce social and mental symptoms of dementia in AD to some degree [46].

Antioxidant agents: selegiline and vitamin E

Current theories suggest that an increase in free-radical formation may occur in AD and have a direct toxic effect. The brain may be vulnerable to the damaging effects of oxidative stress because of an abundance of catecholamine's and a relatively low concentration of antioxidative enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase). Furthermore, Aß has been linked in increased free-radical formation. Vitamin E in doses of 1000 IU orally twice daily and selegiline (a monoamine oxidase B inhibitor) in doses of 5 to 10 mg orally every morning, seem to minimize free-radical damage by acting as free-radical scavengers. [47-50].

Future scenario

The majority of currently ongoing clinical trials are focused on interventions that directly influence the pathologic cascade in AD. AD is a neurodegenerative disease affecting people worldwide. Clinically, it is considered by the presence of extracellular amyloid plaques and intracellular NFTs, resulting in neuronal dysfunction. The currently approved treatments for AD are limited to cholinesterase inhibitors and memantine or the combination of these agents.

CONCLUSION

Given the complexity of AD, treatment of patients remains challenging. It is supported that several new drugs, many have failed larger phase III trials, not meeting efficacy endpoints. Alterations in the concentration of neurochemical, enzymatic and oxidative biomarkers have been observed in individuals with AD. In spite of this complexity in pathogenic events, scientists have identified a large number of drugs that have been able to improve the quality of life of Alzheimer's patients to some extent. Innovative and adaptive clinical trial designs may capture the potential evolution of therapeutic combinations over the long and complex course of disease progression,

Abbreviations

ACHEIs - Acetylcholinesterase Inhibitors

AD - Alzheimer's Disease

APP - Amyloid Precursor Protein

Aß - Amyloid P-Peptide

NFTs - Neurofibrillary Tangles

NMDA - N-Methyl-D-Aspartate

NSAIDS - Nonsteroidal Anti-Inflammatory Drugs

PCD - Prominent Protein-Conformational Disease

PET - Positron Emission Tomography

ROS - Reactive Oxygen Species

SPS - Senile Plaques

SSRIs - Serotonin Reuptake Inhibitors

Consent for publication

Not applicable

Funding

None

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none

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