Available online on 15.05.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Review on Aetiology, Diagnosis and Treatment of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is one of the most common cause of dementia in older adults and an important public health problem. The purpose of this review article is to provide a brief introduction to A D and the related concept of mild cognitive impairment (M C I) and may throw light on the prevalence, causes, treatment, diagnosis and prevention. Vast knowledge regarding disease and disorders will help people take precautions for not getting effected by it. This will help reduce the number of Alzheimer's disease. Since the exact curative treatment has not been established for AD. AD is a complex disorder with environmental and genetic components. There are two major types of Alzheimer's disease, early on set and the more common late onset. The genetics of early-onset Alzheimer's disease are largely understood with variants in three different genes leading to AD disease. In contrast, with several common alleles associated with late-onset Alzheimer's disease, including APOE, have been identified using association studies, the genetics of late-onset Alzheimer's disease are not fully understood. Continuing efforts are still required. This includes development of medicines that would slow progression, halt, or prevent AD and other dementias from occurring. Studies are currently underway to identify biomarkers for diagnosis and new therapeutical agents to prevent or slow down disease progression.

Keywords: Alzheimer's disease, dementia, neuro-degeneration, mild cognitive impairment.

Article Info: Received 25 March 2019; Review Completed 04 May 2019; Accepted 07 May 2019; Available online 15 May 2019

Cite this article as:

Lou Diana MM, Yadav K, Bhutia GT, Owoalade SA, Review on Aetiology, Diagnosis and Treatment of Alzheimer's disease, Journal of Drug Delivery and Therapeutics. 2019; 9(3):626-633 **http://dx.doi.org/10.22270/jddt.v9i3.2835**

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, a fatal neurodegenerative disease where patients suffer from severe cognitive impairments, loss of memory, and the inability to function in later stages.[1] Alzheimer's disease (AD) is characterized by decreased cognition. [2] AD should be differentiated from normal age-related decline in cognitive function, which is more gradual and associated with less disability. AD usually starts with mild symptoms and ends with severe brain damage. People with dementia lose their abilities at different rate.[3]

ALZHEIMER'S DISEASE

History

Alois Alzheimer and Auguste D the German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51-year-old woman with a ' peculiar disease of the cerebral cortex,' who had presented with progressive memory and language impairment, disorientation, behavioural symptoms (hallucinations, delusions, paranoia),and psycho social impairment. [5, 6] Remarkably, many of the clinical observations and pathological findings that Alzheimer described more than a century ago continue to remain central to our understanding of AD today.[7]

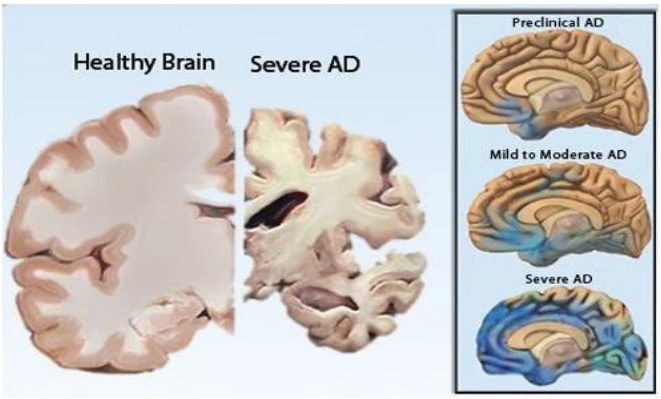

Fig 1: Showing difference between healthy brain and AD brain.[4]

Epidemiology

Although AD was long believed to be a rare disease, awareness of AD prevalence was highlighted in the late 1960s and 1970s by blessed and colleagues and Katzman. Present epidemiological data suggest that dementia, defined as the clinical state of acquired cognitive loss in multiple domains, affects about 5–7% of individuals over age 65 yr .[8] Alzheimer's disease (AD) has affected about 13% of the world's population over the age of 60" (World Alzheimer Report, 2013, p. 1). Between 2010 and 2050, the number is projected to increase from 101 million to 277 million worldwide (World Alzheimer Report, 2013); yet no current cure has yet been found for the disease (Parra-Dames et al., 2014).[9] The world's population is rapidly aging, and the number of people with dementia is expected to grow from 35 million today to 65 million by the year 2030.[10]

Dementia

The team "Dementia" is associated with memory loss and difficulties with thinking, problem solving or language. It is the clinical condition which involves the deterioration of intellectual functions in an individual.[11] various cognitive abilities can be impaired with dementia, including memory, language, reasoning, decision making, visuospatial function, attention, and orientation. Most individuals with dementia, cognitive impairments are often accompanied by changes in personality, emotional regulation, and social behaviours. The cognitive and behavioural changes that occur with dementia interfere with work, social activities, and relationships and impair a person's ability to perform routine daily activities. [12, 13]

Mild cognitive impairment

The MCI Concept MCI is a syndrome characterized by memory and/ or other cognitive impairments that exceed the decline in cognition associated with the normal aging process. MCI is often regarded as a precursor to dementia or a transitional state between healthy cognitive aging and dementia (Fig. 2).[14]

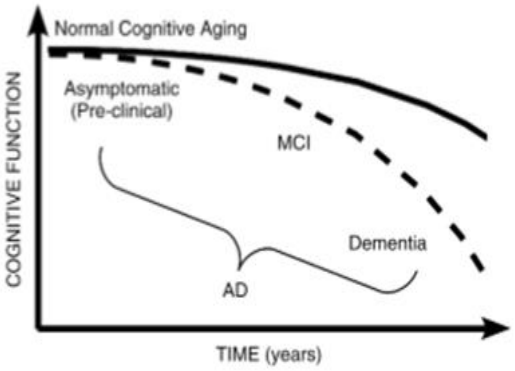

Fig 2: Progressive development of Alzheimer's disease (AD).

The relationship among pre-clinical, mild cognitive impairment (MIC) and Dementia stages of AD (dashed line) are shown relative to normal Cognitive aging (solid line).

PATHOLOGY

The disease is characterized by oxidative stress, mitochondrial impairment, neuro-inflammation, synaptic dysfunction, and blood-brain barrier disruption, which may be caused in part by abnormal extracellular accumulation of amyloid-β peptide part by an abnormal extracellular accumulation of amyloid-β peptide (Aβ) in amyloid plaques and tau protein aggregation in intracellular neuro-fibrillary tangles (NFTs), which are the hallmarks of Alzheimer's disease, causing synaptic and neuronal loss and enhancing cognitive dysfunction .[15]

ETIOLOGY

In the past decade, tremendous strides have been made in determining the multifactorial aetiology of AD; Individuals with Down syndrome (trisomy 21) almost universally develop the neuropathology symptoms of AD after age 40 years.

Three genes have been found to be associated with the development of the early-onset familial form of AD, and one gene is considered as a risk factor most commonly in late-onset form of AD. [16] The 4 genetic loci already known as contributing to AD do not appear to account for all of the genetic risk of the disease. Chromosome 12 is recently suspected of having a susceptibility gene for AD. [17] Mutations within the gene on chromosome 21, which encodes for myeloid precursor protein (APP), the precursor of myeloid beta (AP) peptides, are associated with about 2% to 3% of all cases associated with the early-onset familial form of AD. The presenilin 1 (PSI) gene located on chromosome 14 and the presenilin 2 (PS2) gene located on chromosome 1 are linked to 70% to 80% and 20% to 25% of the early-onset familial form of AD, respectively .[18] The commonality between these 3 genes (ie, APP, PSI, continues to age, and PS2) is that they are increasing; alter APP processing, which leads to increased production of AP prevalence. According to the "amyloid cascade hypo- thesis," AP deposition is the initial critical event in the etiology and pathogenesis of AD; all other features of the disease follow (eg, neurofibrillary tangles, synapse and cell loss, dementia) .[19, 20] Apo lipoprotein E has 3 different forms: E2, E3, and E4. It is a serum lipoprotein involved in cholesterol metabolism that is encoded by a gene (APOE) on chromosome 19. This is the only gene known to be associated with the more common late- onset forms of AD (familial and sporadic), accounting for 50% of the risk of AD. It is the inheritance of the E4 allele that confers the risk. Individuals with homozygous form of E4 allele (E4/E4) are more likely to develop and have an earlier age of onset of AD than are those individuals with other genotypes of individuals with APOE alleles. The carriers of the E4 allele, however, show no cognitive impairment, % where as people without the E4 allele can develop AD. [21]

Current etiological hypothesis of AD

The neuropathological features of both forms of AD are characterized by abnormal extracellular accumulation of myeloid-β peptide (Aβ) in Amyloid plaques and tau protein aggregation in intracellular neurofibrillary tangles (NFTs). [22]

The Amyloid Hypothesis

The main hypothesis of AD pathogenesis is the Amyloid cascade hypothesis, positioning amyloid aggregation as the mechanistic initiation event, where different stages of abnormal aggregates, from soluble oligomers to insoluble fibers or plaques, cause impaired synaptic function and neuronal damage that results into chronic neuro-degeneration characterized by cognitive impairment and ultimately dementia .[23] In this hypothesis, the accumulation of Aβ plaques acts as an enhancer in the pathological cascade, including neurite damage and neuro fibrillary tangle (NFT) formation via tau protein, which may results to neuronal dysfunction and cell death in AD. Genetic, biochemical, and pathological evidence support the amyloid

cascade hypothesis, which postulates that the accumulation and aggregation of Aβ plaques is the main cause of AD.[24]

The Tau Hypothesis

Tau proteins are mainly found in neurons and belong to the family of microtubule-associated protein (MAP); they develop long processes such as axons and dendrites for neuronal transmission. In the adult brain six tau protein iso-forms derived by alternative splicing of gene have been identified; they are located on the long arm of chromosome 17.Tau protein deposition in an insoluble aggregates results in a loss of tau function, leading to microtubule instability and promoting neurodegeneration. Intact microtubules are required for axonal transport and normal neuronal function; it has long been recognized that microtubule destabilization causes AD. [25]

The Cholinergic Hypothesis

For many years, the cholinergic hypothesis has been the centre of study dementias and other neurodegenerative diseases. Acetylcholine is a neurotransmitter that is responsible for the conduction of electrical impulses from one nerve cell to another. [26] It has been proposed that the AChE produces non-cholinergic functions such as formation of NFTs and as Aβ deposition in the brain of AD patients. [27]

The Mitochondrial Cascade Hypothesis

The mitochondrial cascade hypothesis has been associated with mitochondrial DNA (mtDNA) mutations, oxidative stress, and the presence of Aβ in mitochondria, which plays an important part in AD pathogenesis, because this induces mitochondrial dysfunction and neuronal apoptosis .[28] The (mtDNA) mutations include CD2-associated protein, which induces mitochondrial fission and transport damage along axons due to dynamic actin remodelling. [29] APP could be used to regulates the mitochondrial Aβ levels, which may be targeted to the outer mitochondrial membrane and interfere with protein import. [30]

The Metabolic Hypothesis

The metabolic hypothesis states that the disease is caused by some changes in metabolic processes such as obesity, diabetes, hypercholesterolemia, and others. Recent research suggests that there are strong relationships between AD and type 2 diabetes mellitus (T2DM). [31] The pathogenetic mechanisms through which T2DM causes cognitive impairment are not clearly established. The proposed scenarios connecting diabetes and dementia are numerous; they include vascular lesions, inflammation, oxidative stress, elevated glycolysis end products, insulin resistance, abnormal insulin receptor signalling, insulin degradation, and insulin's relationship with Aβ-deposits. [32] Many researches support the hypothesis that AD responds to pathogenesis based on neuronal energy alterations, which are caused by insufficiencies in the glucose function. Metabolic abnormalities are mainly associated with brain insulin growth factor, which regulates energy production and insulin resistance.[33]

The Vascular Hypothesis

Vascular hypothesis basic principle is characterized by the reduction of cerebral blood flow. This hypothesis suggests that the neurodegenerative process is initiated by chronic cerebral hypo perfusion caused by aging, oxidative stress, and vascular conditions such as hypertension, atherosclerosis, and hyper cholesterolemia. [34] Hypo perfusion and hypoxia are one of the problems, but the breakdown of the blood-brain barrier also results in accumulation of neurotoxic serum proteins in the brain, inflammation, as well as vascular and synaptic dysfunction, which leads to defects in Aβ and Tau metabolism and clearance, which in turn cause vascular problems. [35] BBB dysfunction mediates the indirect neurotoxic effects of chronic hypoper fusion by promoting oxidative stress, inflammation and impaired glucose transport across the blood-brain barrier, and their permeability. [36]

CAUSES OF ALZHEIMER'S DISEASE

The main cause for this disease is still not known, with age as the greatest risk factor. [37]

Genetic Mutations

Changes in DNA have been associated with the development of neuro-degeneration; such changes may be controlled by epigenetic factors and also by hereditary changes, representing the familial form or "sporadic" mutations. Changes in mitochondrial pathways, protein degradation, free radical and oxidative stress control, and immune system functions may be induced by Genetic mutation. These genetic mutations affect cell function, allowing apoptosis and inducing neuro-degeneration. [38,39]

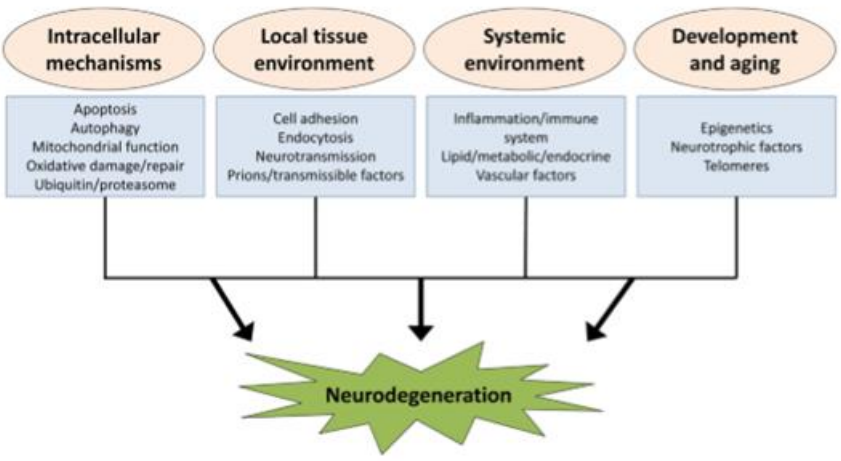

Fig 3: Pathway to neurodegeneration in AD .[40]

Protein misfolding

Neurodegenerative diseases is associated with protein misfolding, a process which is related with genetic mutations or triggered by external factors that induces incorrect structural protein formation and function. It subsequently leads to their aggregation in oligomer form and in some cases as plates, stored intra cellularly, extracellular (Alzheimer's disease). [41]

Protein Degradation

Pathways Intracellular misfolded proteins maybe regulated by a degradation system called the polyubiquitination-proteasome system. This system will select misfolded protein and forms an ubiquitin polymer with the protein, by ubiquitin ligase enzyme. The ubiquitinated protein is transported to the proteasome and degraded into small fragments, however, when these degradation pathways fail in the degradation of misfolded proteins, cell damage can be induced by oxidative stress and generation of toxic molecules. [42]

Mitochondrial Dysfunction

The mitochondrion is an organelle, responsible for providing energy (ATP) to the cell, through the electron transport chain. Reactive oxygen species can induce oxidative stress by two pathways of damage: the electron transport chain and mtDNA. Those changes induce mitochondria dysfunctions, membrane lipid peroxidation, and decreased ATP calcium homeostasis compromise and mitochondrial permeability.

This dysregulation also induces the intrinsic mitochondrial apoptotic pathways through the separation of the anti-apoptotic protein Bax/Bcl2 complex, allowing the Baxprotein to carry out an interaction with a voltage-dependent channel for opening and permeability for calcium transition, processes which induce mitochondrial fragmentation. Eventually, cytochrome C is released from the mitochondria, and caspase 9 is activated; this in turn activates caspase 3. The activation of the caspases triggers programmed cell death. Another result which is related to mitochondrial dysfunction has been associated with the increase in free radicals and oxidative stress, which induces neuro degeneration. [43]

Neuro-Inflammatory Processes

The inflammatory process in the central nervous system includes the activation of astrocytes, T-cell infiltration, microglia cells, cytokine release, and major histo compatibility complex class II expression. The activation of the inflammatory process may be because of the extracellular aggregation of misfolded proteins, cellular debris as a product of neurodegeneration, oxidative stress, and other external agents.[44]

Role of environment for AD

Several studies state a role for environmental effects on AD development. Richard Mayeux and Yaakov Stern recent review summarized the role of diet, activities, or diseases that potentially play a role in the onset of Alzheimer disease. Diabetes, dyslipidemia hypertension, obesity and smoking, all have been found to increase risk as well as the history of brain trauma, cerebrovascular disease, and vasculopathies. Also A higher level of education is included, hence mediterranean diet were shown to decrease the risk of developing AD.[45]

Table 1: Factors that modify the risk of Alzheimer disease

Antecedent	Direction	Possible Mechanism
Cardiovascular disease	Increased	Parenchymal destruction Strategic location Increase alpha beta deposition
Smoking	Increased	Cerebrovasular effect Oxidative stress
Hypertension	Increased and decreased	Micro-vascular disease
Type 2 diabetes	Increased	Cerebrovascular effect Insulin and alpha beta compete for clearance
Obesity	Increased	Increased risk of type 2 diabetic inflammatory
Traumatic head injury	Increased	Increase alpha beta and amyloid precursor protein desposition
Education	Decreased	Provides cognitive reserve
Leisure activity	Decreased	Improves lipid metabolism,mental stimulation
Mediterranean diet	Decreased	Antioxidant, anti-inflammatory
Physical activity	Decreased	Activates brain plasticity,promotes brain vascularisation

Source; Epidemiology of Alzheimer Disease Richard Mayeux and Yaakov Stern cold spring Harb Perspect Med 2012;2.

RISK FACTORS

Known risk factors for AD include age and genetic factor; other possible risk factors are level of education, female sex, history of head injury, exposure to heavy metals and toxins, positive family history, and trisomy. [46, 47] the $\varepsilon 4$ allele is the risk allele and is the most significant known genetic risk factor for LOAD. This allele was first identified as a genetic risk factor for LOAD in 1993 by Corder et al, The association for this allele has been replicated numerous times in various ethnic groups including Caucasians, Although AD risk is much higher in persons with one or more $\varepsilon 4$ alleles, $\varepsilon 4$ is not causative and some individuals homozygous for $\varepsilon 4$ never develop AD. [48] African Americans [49, 50] Hispanics and Asians [51, 52] the $\varepsilon 4$ allele is the only widely accepted genetic risk factor for LOAD. [53] and increases risk with increasing $\varepsilon 4$ dosage. In contrast to decreases AD risk Possible APOE genotypes, listed in order of AD risk, are Possible APOE genotypes. [54]

DIAGNOSING OF ALZHEIMER'S DISEASE

An autopsy-based (post-mortem) pathological evaluation is a gold standard for AD diagnosis. The presence and distribution of amyloid plaques and NFT in the brain is used to establish the stage the disease and diagnosis of definitive AD stage the disease. [55] in clinical settings, the doctors can be able to diagnose this disease with the help of taking medical history and neurological examinations. The accuracy for these diagnoses would be about 70-90% right. Alzheimer's disease is usually diagnosed when there are cognitive or behavioural (neuropsychiatric) symptoms. [56]

Biomarkers

There are several biomarkers approach which can be used to study Alzheimer's disease. Biomarkers are required to select patients during studies and also to identify high risk patients for early treatment as well as monitoring the patient's disease progression or response to treatment. The biomarkers include: - Magnetic Resonance Imaging (MCI), Positron emission tomography, fluid biomarkers etc.

Magnetic Resonance Imaging

This involves the use of radio frequency waves and strong magnetic field, and measures the energy released by protons in various tissues and parts of the brain. The study of the regional patterns of brain atrophy in patients can be achieved by this method.

Positron Emission Tomography

It is a technique which uses nuclear imaging and it also helps to measure the regional brain metabolism. The earliest signs of Alzheimer's disease can also be detected.

Fluid Biomarkers

It's based on the blood plasma and the CSF**.** They are used for diagnosis purposes as well. [57] Several studies have been conducted using immunoassays to measure the levels of various proteins in the CSF, finding that patients with AD show decreased levels of the 42 amino acid isoform of the Ab (Ab-42) peptide and elevated levels of the phosphorylated tau (P-tau) peptide.[58, 59]

Treatment

Drug therapy for the AD is still in its infancy, till now there is no cure for AD, and drug therapy for the disease is still in its infancy. The approved medications for the treatment of probable AD is limited in controlling the symptoms of AD but do not slow down the progression or reverse the course of the disease. [60] FDA approved 5 drugs for treatment of AD symptoms. These approved drugs are able to treat symptoms of mild-to-moderate cases but do not slow down the progression of the disease. They work to either increase levels of acetylcholine, a protein important for memory and thinking, by inhibiting an enzyme responsible for its breakdown or by regulating levels of the brain protein glutamate, which accumulate in people with AD and kills brain cells. In a recent study, researchers found that one of these, Aricept, led to a 6-month delay in further symptoms. [61]

Cholinesterase inhibitors

Cholinesterase inhibitors are class of medicinal agent that block cholinesterase, which is an enzyme that breaks down the neurotransmitter acetylcholine. AD is linked with low levels of acetylcholine, hence inhibiting or blocking the breakdown of acetylcholine through cholinesterase inhibitors may help to improve brain function. [62]

Glutamatergic agents

A glutamatergic NMDA receptor blocker, known as memantine is an effective agent used in treating severe AD. This drug was first approved in Germany since 1970's, but clinical trial data to support its use have been limited. Therefore recent clinical trials data for investigating the safety and clinical efficacy of memantine show that it is effective for moderate to severe AD. The medication is still being studied and is approved in the United States and several European countries. Current Pharmaceutical Products "Pipeline" for AD Treatment

Table 2: New medicines in development for Alzheimer disease

Drug Name	Indication	Company	Development Status
ABT-126 acetylcholinesterase inhibitors	Alzheimer disease	Abbott	Phase 2
ABT-126	Alzheimer disease	Abbott	Phase 2
LY2886721	Alzheimer disease	Eli Lilly and Company	Phase 1
AZD3480	Alzheimer disease	Targacept InC.	Phase 2
AVP-923(dextromethorph an/quinidine)	Alzheimer disease, mild cognitive impairment	Avanir Pharmaceuticals	Phase 2
MABT5102A	Alzheimer disease	Genentech	Phase 2
AZD5213	Alzheimer disease	AstraZeneca	Phase 2
Gantererumab	Alzheimer disease	Hoffmann-La Roche	Phase 3
AAB-003(PF-05236812)	Alzheimer disease	Pfizer	Phase 1
BMS-241027	Alzheimer disease	Bristol-Myers Squibb	Phase 1
MABT5102A	Alzheimer disease	Genentech	Phase 2
BIIB037	Alzheimer disease	Biogen Idec	Phase 1
GSK2647544	Alzheimer disease	GlaxoSmithKline	Phase 1

The beneficial effects of nutraceuticals A study conducted by Trully in 2002 with 148 subjects with dementia and 45 healthy controls found that the serum docosahexaenoic acid (DHA) of AD subjects were significantly decreased. [63] The DHA is the main omega 3 polyunsaturated fatty acid (O-3 PUFA) amongst eicosapentaenoic acid (EPA). Evidences suggest that body low levels of O-3 PUFAs may be associated with the development of neurodegenerative diseases, including AD. Large scale intake of O-3 PUFAs can lower the risk of AD and slower cognitive decline related to age. [64]

PHYSICAL ACTIVITY AND AB- INDEPENDENT MECHANISMS

Several studies have shown that physical activity can also improve cognitive function in AD and MCI patients through Aβ-independent mechanisms. It has been shown that physical activity increases neurotrophic factors such as BDNF levels in the brain and through their neuro-protective effects improve cognition in AD (Erickson et al., 2012). Also, regular physical activity acts as a pre-conditioner against oxidative stress and reactive oxygen species production (ROS).

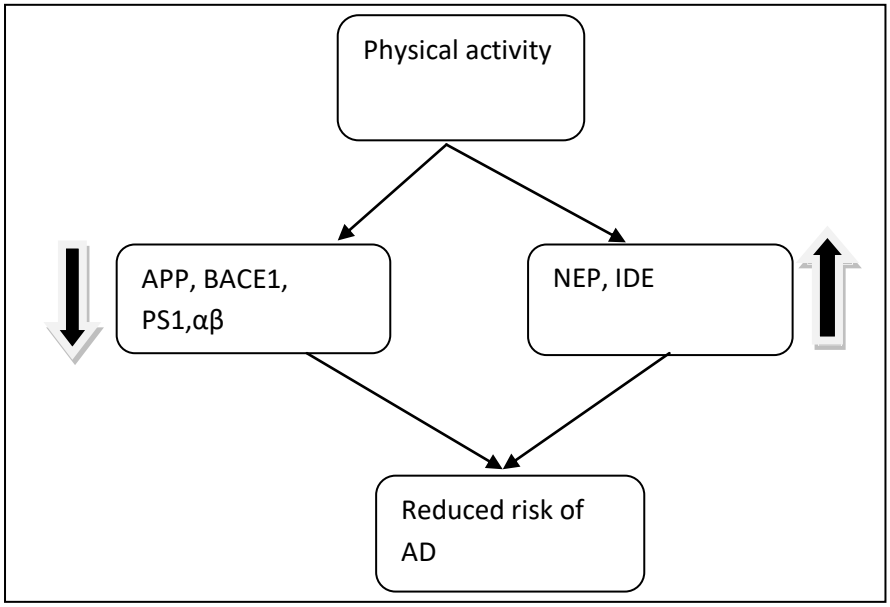

Fig 4: Mechanisms of physical activity in prevention of Alzheimer's disease risks. [65]

PSYCHIATRIC MANAGEMENT OF NON-COGNITIVE SYMPTOMS

Early intervention is important since psychiatric symptoms can respond to treatment more readily than cognitive and functional deficits.[66]

Table below shows the behavioural clusters manifested in AD and relevant classes of medications for intervention.

Table 3: Behavioural clusters Matched with potentially Relevant Classes of Medication

Behaviour	Agent
Agitation/aggression	Antipychotics, anticonvulsants, antidepressants, anxiolytics
Anxiety	Antidepressants, anxiolytics, anticonvulsants
Apathy	Antidepressants, stimulants
Disturbed effect/mood	Antidepressants, anticonvulsants
Altered ideation/mood	Antisepsychotics
Vegetative Features	Antidepressants, anxiolytics, stimulants.

Source: American psychiatric association Practice guidelines for the treatment of Alzheimer Disease and Other dementias of Late Life

CONCLUSION

Early prevention in preclinical stages is the most effective way to protect brain and reduce risk of. It seems that physical activity especially aerobic exercise is one of these preventing factors. New funding models should be explored which can support core research facilities and non-tenured staff in academic institutions, such as the creation of endowments for facilities and pharmaceutical and biotech consortia. Innovation is needed to encourage diversity of approaches to fight AD. In 2012, dementia was declared a public health priority by the World Health Organization (WHO). The number of patients with Alzheimer disease will rise significantly Due to the ageing of the world population. If no treatment is available, this will result to a major health issue with enormous financial burdens to health care systems.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

ACKNOWLEDGMENTS

Authors are thankful to the management of the department of pharmacology, Karnataka college of Pharmacy, Bangalore, Karnataka, India for providing necessary materials, information and ideals regarding the study.

REFERENCES

1. Raymond C, Linda Z. Current neuroimaging techniques in Alzheimer's disease and applications in animal models. Am J Nucl Med Mol Imaging .2012; 2(3):386-04.
2. Mark T, Perry G. Review Article Genetics of Alzheimer's disease. Bio Med Research International.2013; 7(1):1-13.
3. Gross A, Jones R, Habtemariam D, Fong T, Tommet D, Quach L, Schmitt E, Yap L, Inouye SK. Delirium and Long-term Cognitive Trajectory Among Persons With Dementia. Arch Intern Med. 2012; 172(17):1324-31.
4. Sheldon F, Shaffer J, Petrella J, Choudhury K, Calhoun V, Coleman R, Doraiswamy P. alzheimer's Disease Neuroimaging Initiative. Predicting Cognitive Decline in Subjects at Risk for Alzheimer Disease by Using Combined Cerebrospinal Fluid, MR Imaging, and PET Biomarkers. Radiology. 2013; 266(2):583-91.
5. Alzheimer A. Uber eine eigenartige Erkrankung der Hirnridne. About a Peculiar Disease of the Cerebral Cortex. Allg Z Psychiatr. 1907; 64: 146-48.
6. Alzheimer A. About a peculiar disease of the cerebral cortex. Alzheimer Dis Assoc Disord. 1987; 1(3); 8.
7. Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. Lancet .1997; 349(9064): 1546.

8. Alan J. Lerner, Women and Alzheimer's disease. The Journal of Clinical Endocrinology & Metabolism. 1999; 84(6); 1830-1834.
9. Edith, Samuel. Recent Research and Updates on Alzheimer's disease. Journal of Psychology and Behavioural Science.2014; 2(2); 103-12.
10. Korole v, Igor O. Alzheimer's disease. A Clinical and Basic Science Review. Medical Student Research Journal; 2014; 04(9); 024-033.
11. Reshma H .Alzheimer's Disease- A Review, J. Pharm. Sci. & Res.2016; 8(11): 1292-94.
12. Gilman S. Oxford American handbook of neurology. Oxford University Press: Oxford, UK; 2010.ISBN 10: 0195369793 ISBN 13: 9780195369793.
13. Hyman B , Jack C , Kawas C , McKhann G , Knopman D, Chertkow H. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement .2011; 7(3):26-39.
14. Seeley W, Kim E , Rabinovici G D, Gorno-Tempini M L, Rascovsky K, Pagliaro TA. Distinct MRI atrophy patterns in autopsy-proven Alzheimer's disease and front to temporal lobar degeneration.Am J Alzheimers Dis Other Dement .2007; 22:474-88.
15. Van Broeckhoven C, Van Cauwenberghe C, Sleegers K. The genetic landscape of Alzheimer disease. Clinical implications and perspectives. Genet Med. 2016; 18:421-30.
16. Filley C M. Alzheimer's disease in women. Am J Obstet Gynecol. 1997; 176:1-7.
17. Bass M P, Pericak-Vance MA, Yamaoka LH. Complete genomic screen in late-onset familial Alzheimer's disease: evidence for a new locus on chromosome 12. JAMA. 1997; 278:1237-41.
18. Hardy J. The Alzheimer family of diseases: many etiologies, one pathogenesis Proc Natl Acad Sci USA. 1997; 94:2095-97.
19. Singh V K. Neuroautoimmunity: pathogenic implications for Alzhei- mer's disease. Gerontology. 1997; 43:79-89.
20. Singer S J, Delvji N N. Genetic clues to Alzheimer's disease. Science. 1996; 271:159-60.
21. Lendon C, Goate A M, Ashall F. Exploring the etiology of Alzheimer disease using molecular genetics. JAM. 1997; 277:825-31.
22. Hasegawa M. Molecular Mechanisms in the Pathogenesis of Alzheimer's disease and Tauopathies-Prion-Like Seeded Aggregation and Phosphorylation. Biomolecules. 2016; 6(2):24.
23. Schöll M, Hansson O, Zetterberg H ,Blennow K, Mattsson N. Amyloid biomarkers in Alzheimer's disease. Trends Pharmacol Sci. 2015; 36:297-09.
24. Barage S H, Sonawane, K D. Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. Neuropeptides. 2015; 52:1-18.
25. Khan A, Kalra J. Reducing AÎ^2 load and tau phosphorylation: Emerging perspective for treating Alzheimer's disease. Eur J Pharmacol. 2015; 764:571-581.
26. Singh B, Anand P. A review on cholinesterase inhibitors for Alzheimer's disease. Arch Pharm Res. 2013; 36: 375-99.
27. Jellinger K A. Basic mechanisms of neurodegeneration: a critical update. J Cell Mol Med. 2010; 14:457-87.
28. Saykin, Ramanan VK. Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer´s disease, Parkinson´s disease, and related disorders. Am J Neurodegener Dis. 2013; 2:145-75.
29. Beal M F, Lin M T. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006; 443:787-95.
30. Harrison F E Walker J M. Shared Neurophatological Characteristics of Obesity, Type 2 Diabetes and Alzheimer´s Disease: Impacts on Cognitive Decline. Nutrients. 2015; 7: 7332-57.
31. Mattson M P, Kapogiannis D. Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. Lancet Neurol. 2011; 10: 187-98.
32. Marschoff E R, Gonzalez S E Domínguez R O, Pagano M A, Repetto M G, et al. Alzheimer disease and cognitive impairment associated with diabetes mellitus type 2 associations and hypothesis. Neurología. 2014; 29:567-72.
33. Soiza R L, Kelleher R J. Evidence of endothelial dysfunction in the development of Alzheimer's disease: Is Alzheimer's a vascular disorder. Am J Cardiovasc Dis. 2013; 3:197-26.
34. Karran E, De Strooper B. The Cellular Phase of Alzheimer's disease. Cell. 2016; 164:603-15.
35. Di Marco LY, , Evans PC, Marzo A ,Venneri A, Farkas E. Neurobiology of Disease Vacular dysfunction in the pathogenesis of Alzheimer´s disease – A review of endothelium mediated mechanisms and ensuing vicious circles. Neurobiol Dis. 2015; 82:593-606.
36. Janota C, Brito M A, Lemere CA. Dissecting the Contribution of Vascular Alterations and Aging to Alzheimer's disease. Mol Neurobiol. 2016; 53: 3793-811.
37. Busse A. Mild cognitive impairment long-term course of four clinical subtypes. Neurology.2006. 67(12):2176-85.
38. Tanzi R E, Bertram L. The genetic epidemiology of neurodegenerative disease. J Clin Invest. 2005; 115:1449-57.
39. Coppedè F, Migliore L. Genetics, environmental factors and the emerging role of epigenetics in neurodegenerative diseases. Mutat Res. 2009; 667: 82-97.
40. Andrew J Saykin, Vijay K. Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson's disease, and related disorders. Am J Neurodegener Dis 2013; 2(3):145-75.
41. Nestler EJ, Malenka RC, Hyman SE. Molecular Neuropharmacology: Neurodegeneration. China: McGraw-Hill. 2009.
42. Di Mauro S, Schon EA. Mitochondrial disorders in the nervous system`Annu Rev Neurosci. 2008; 31:91-123.
43. Glass C K, Saijo K, Gage F H, Winner B, Marchetto MC. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010; 140: 918-34.
44. Richard Mayeux and Yaakov Stern .Epidemiology of Alzheimer Disease. Stern Cold Spring Harb Perspect Med 2012; 2(8):1-18.
45. Lendon C L, Goate A M, Ashall F. Exploring the aetiology of Alzheimer disease using molecular genetics. JAM. 1997; 277:825-31.
46. Gilnian S. Alzheimer's disease. Perspect Biol filed. 1997; 40:230-45.
47. Knight J A. Reactive oxygen species and the neurodegenerative disorders. Am Clin Lab Sci. 1997; 27:11-25.
48. Saunders AM, Strittmatter WJ. "Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families,"Science.1993; 261(.5123):921– 23.
49. Hendrie HC, Hui S, Hall KS, Apolipoprotein E genotypes and Alzheimer's disease in a community study of Bio Med Research International 9 elderly African Americans,"Annals of Neurology;1995;37(1):118–20.
50. Ottman GR, Stern Y. "Apolipoprotein E and Alzheimer's disease: ethnic variation in genotypic risks,"Annals of Neurology.1995; 37(2):254–59.
51. Noguchi S, Yamada N, K. Murakami. "Apolipoprotein E genotype and Alzheimer's disease," The Lancet; 1993; 342(8873):737–38.
52. Kawano M, Ueki A, Namba Y, Kawakami M, and Ikeda K. "A high frequency of apolipoprotein E4 isoprotein in Japanese patients with late-onset non familial Alzheimer's disease, Neuroscience Letters. 1993; 163(2):166–68.
53. Abraham, D. Harold, P. Holling worth. "Genome wide association study identifies variant sat CLU and PICALM associated with Alzheimer's disease. Nature Genetics.2009; 41:1088–93.
54. Corder EH, Risch NJ, Saunders AM. "Protective effect of apolipo-protein E type 2 allele for late onset Alzheimer disease .Nature Genetics.1994; 7(2):180–84.
55. Mc Khann. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia. 2011; 7(3): 263-69.
56. Braak H, Thal D R, Del Tredici K, Ghebremedhin E. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol 2011; 70:96-09.
57. Guhne U, Busse A, Hensel A, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. Neurology .2006; 67:217685.
58. Weigand S D, Shaw L M ,Vemuri P, Wiste H J, Trojanowski J Q, Weiner M W. MRI and CSF biomarkers in normal, MCI, and AD subjects: diagnostic discrimination and cognitive correlations. Neurology .2009; 73:287-93.
59. Weiner M W, Beckett L A, Cairns N J, Green R C, Veitch D P, Aisen P S. The Alzheimer's disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dement. 2012; 8: S168. 09.172.

60. Roche H M, Doyle R, Tully A M. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case–control study. Br J Nutr. 2003; 89:483-89.
61. Morris M C, Bienias J L, Evans D A. Dietary intake of antioxidant nutrients and the risk of incidence Alzheimer disease in a biracial community study. JAMA. 2002; 287:3230-37.
62. Colacicco A M, Solfrizzi A, D'Introno A. Dietary intake of unsaturated fatty acids and age-related cognitive decline: A 8.5-year follow-up of the Italian Longitudinal Study on Aging. Neurobiol Aging. 2006; 22(6):282-286.
63. Phillips M A, Calder P C Childs C E. No Effect of Omega-3 Fatty Acid Supplementation on Cognition and Mood in Individuals with Cognitive Impairment and Probable Alzheimer's disease: A Randomised Controlled Trial. Int J Mol Sci. 2015; 16(10):24600-13.
64. Bullock R. Drug Treatments in Alzheimer Disease. Alzheimer's disease International. Fact sheet 8. Revised April 2000. Last accessed April 1, 2004. http://www.alz.co.uk/alzheimers/treatment.html
65. Roecklein K A, Erickson K I, Miller D L. The aging hippocampus: interactions between exercise, depression, and BNDF. Neuroscientist. 2012; 18:82-97.
66. Patrick D. McGorry, Eóin Killackey, Alison Yung. Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry. 2008 Oct; 7(3):148–156.