Original Article
ISSN (Print) : 0971-6580
Toxicology International, *Vol 28(4), 311-316, October -December 2021, DOI: 10.18311/ti/2021/v28i4/27338* *ISSN (Online) : 0976-5131*

Overview on Alzheimer's Disease

Marshet Getachew Argaw and Nagaraju Bandaru*

Department of Pharmacology, College of Pharmacy, Koneru Lakshmaiah Education Foundation, Vaddeswaram – 522502, Andhra Pradesh, India; marshetgetachew120@gmail.com, bnrajupharma@gmail.com

History: Received 2021-03-16; Accepted 2021-11-11; Published 2021-12-22

Abstract

The world wide spread dementia of Alzeheimer disease is estimated to be as high as 24 million and it is hypothesized to be double every 20 years through 2040 resulting to a costly risk of the disease. Alzehimer disease is the main cause of dementia and is manifested by a gradual loss of cognitive function which is initially begin with deterioration of memory. Before death, the patient is fully dependent on their care givers. The main mechanism underlying the neuropath logical changes in Alzheimer patient are remaining unknown. But mainly they may be affected by both environmental and genetic factors. The hall mark pathology of Alzheimer disease are mainly accompanied by the presence of reactive microgliosis and the loss of neurons, white matter and synapses[3].

Keywords: Dementia, Deterioration of Memory, Loss of Cognitive Function, Reactive Microgliosis, Synapses, White Matter

1. Introduction

Alzheimer's is a degenerative disease characterized by dementing disorder at the starting shows mild memory impairment that progresses unrelentingly to a total weakening loss of mental and physical facilities. The most distinguishing lesion present in the disease brain are the neuritic senile plaque and neuro fibrillary tangles as explained by Alois Alzheimer. The significant pathological feature includes neuronal and dendritic loss, neuropil threads, dystrophicneurites, and granulovacuolar degeneration. In addition to this hirano bodies, cerebro vascular amyloid atrophy of the brain are also the main pathological feature of Alzheimer[1]. Alzheimer disease now a day is a relentless neurologic deterioration accompanied by hall mark pathology[2].

2. Etiology

Advanced age, family history is the main risk factor for Alzheimer disease. Studies done on twin and family shows that hereditary factor estimated to play a vital role in at least 80% of Alzheimer disease cases. The inheritance of Alzheimer disease is characterized by formation of dictomatous pattern. On one hand atypical mutations in APP, PSEN1and PSEN2 exhibit early onset (<60 years) familial Alzheimer disease which shows approximately 5% of Alzheimer disease. On the other hand, common gene polymorphisms like the E4 and E2 variants' of APOE gene can affect susceptibility nearly 50% of the common late onset type of Alzheimer disease. These APOE genes are responsible for 30–50% inheritance of Alzheimer disease[4].

3. Clinical Presentation of Alzheimer Disease

In order to diagnose Alzheimer disease clinical evidence of memory loss and impairment of at least one another cognitive domain with evidence of social and occupational function. Alzeheimer disease should be separated

*Author for correspondence

from other case of dementia like vascular dementia, dementia with lewy bodys, Parkinson disease with dementia, fronto temporal dementia and reversible type of dementia. Differences in initial clinical presentation is probably expected based on the brain region affected. The malfunction of an area like speech, personality and judgment, vision, association with sensory motor function in addition to memory loss are well known[5].

With all type of plaque. The second major hall mark that is NFT is rarely has a descriptors like globes and pretangles and has assigned importance based on their location within the brain[5].

4. Pathology

The unique lesion found within the diseased brain are the senile plaques and NFTS. The neuritic plaque is the

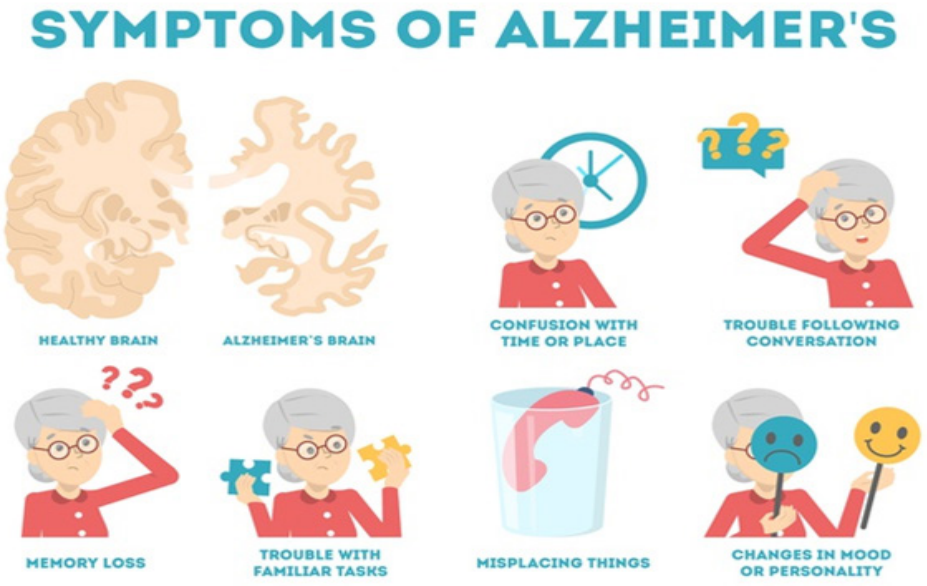


Figure 1. Symptoms of Alzheimer's disease.

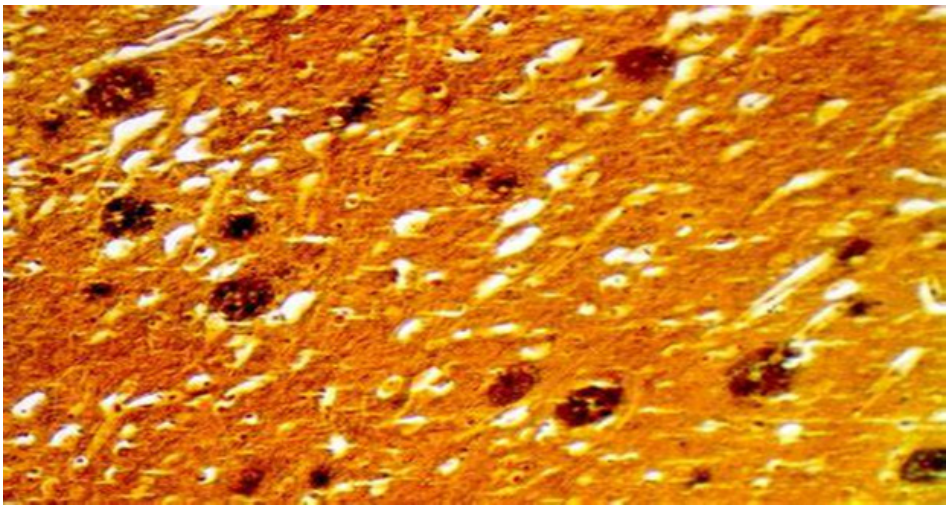


Figure 2. Histopathology of Alzheimer's disease brain.

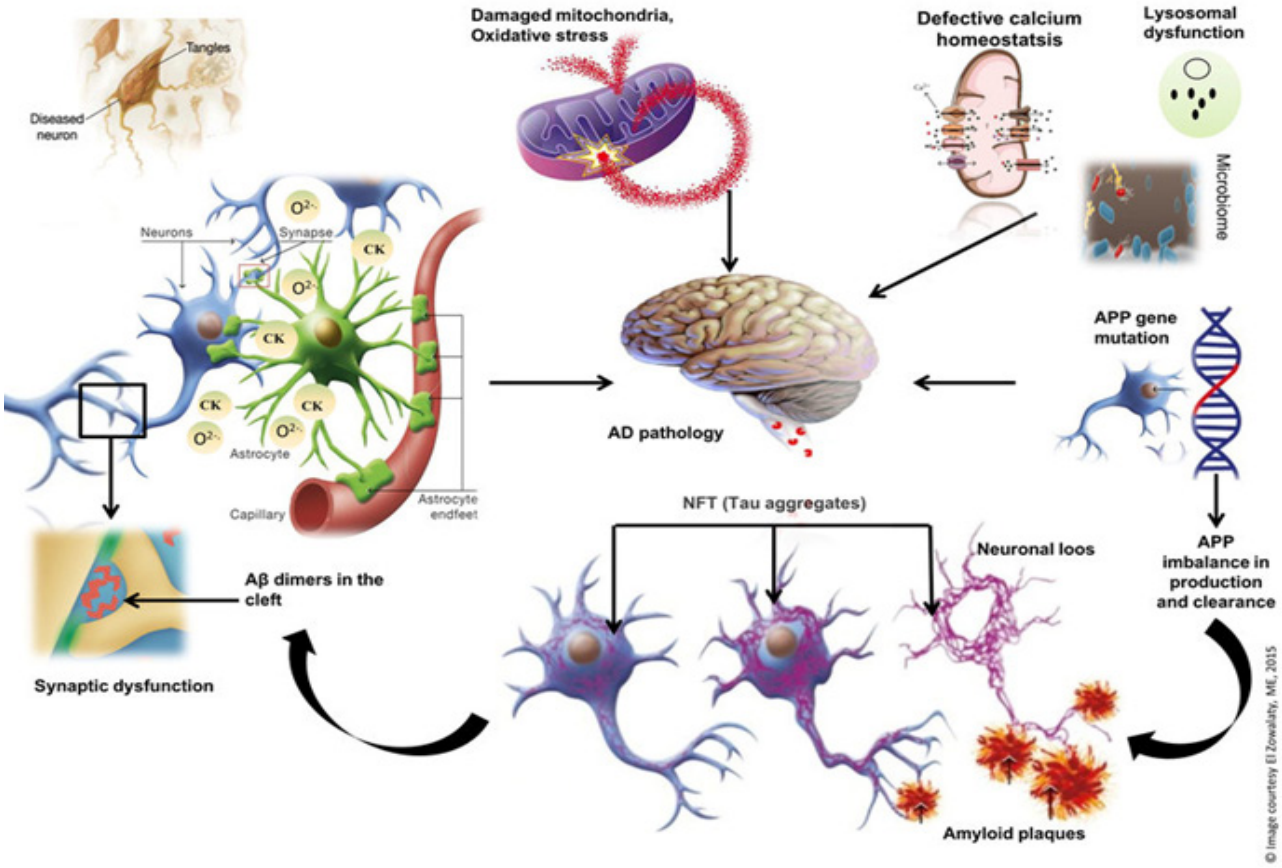


Figure 3. Pathophysiology of Alzheimer's disease.

most relevant and main parameter for the diagnosis of Alzheimer disease at autopsy. The brain region is checked via Bielschosky silver technique which is nonspecific impregnation that reacts.

5.1 Acetyl Choline Esterase Inhibitor (ACE Inhibitor)

FDA approved drug for the treatment of Alzheimer disease inhibit the function acetyl choline in order to increase the level of neurotransmitter called acetyl choline which scarcely present in a brain cell which is affected by Alzheimer or it also oppose or antagonize the role of NMDA type glutamate receptors in order to prevent divergent neuronal stimulation[6].

5.2 Focusing on Aβ

Studies have been done either to decrease the production or to enhance the clearance of Aβ. Active immunization against Aβ cleared amyloid plaque in hAPP transgenic mice shows an effort to decrease Aβ [6].

5.3 Focusing on Tau

Methylene blue was originally thought to inhibit the tau-tau interaction but it also decreases soluble tau by other mechanisms[6].

5.4 Pathopysiology

Alzheimer has a complex and multifactorial pathopysiology. The distinctive pathological feature is accumulation of amyloid cerebral plaque, and neuro fibrillary tangles of abnormally insoluble tau which is an axonal protein. Cholinergic neuronal involvement leads to the decrease in synaptic level of acetyl choline. In addition to these mitochondrial dysfunction, oxidative stress, inflammation, ischemia, insulin signaling, loss of

neuronal synapse, and cholesterol metabolism can also cause Alzheimer[7].

5.5 Non-pharmacological Treatment

The prevention strategies for Alzheimer disease include

- Treatment of hypertension
- consumption of omega- 3 fatty acid
- Physical exercise and cognitive engagement[7].

5.5.1 Pharmacological Treatment[7]

5.5.1.1 FDA-approved Drugs for Alzheimer's

There is no cure for Alzheimer's disease but there are five prescription drugs recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of its symptoms.

The three namely:

- Donepezil
- Galantimine and rivastigmine belongs to the class of choline esterase inhibitors. These drug helps to prevent the breakdown of chemical messenger in the brain which is vital for learning and memory.

Memantine which is under the fourth category is also essential for regulating the activities of various chemical messenger which is also needed for memory as well as learning.

The last category is the combination of drug from acetylcholine esterase inhibitor like donepezil with that of memantine.

5.6 Acetyl Choline Esterase Inhibitor (ACE inhibitor)

In order to treat mild to moderate Alzheimer disease acetyl choline esterase inhibitor is the first line agent[7].

5.6.1 Mechanism Action of Acetylcholine Esterase Inhibitor

It is given to treat symptoms which is related to memory, thinking, language, judgment and other thought processes. The commonly used acetylcholine esterase inhibitor is:

- Donepezil its brand name is Aricept, which is approved by FDA to treat all stages of Alzheimer's disease.
- Galantamine its brand name is Razadyne, which is approved by FDA to treat mild-to-moderate stages.
- Rivastigmine Exelon approved by FDA to treat mild-to-moderate Alzheimer's and mild to moderate dementia related with Parkinson's disease.

Mechanism action of acetylcholine esterase inhibitor act by enhancing the levels of acetylcholine which is a chemical messenger important for in memory, judgment and other thought processes. Different brain cell release neurotransmitter which is used to transport impulse to other cells. After the impulse arrived to the receiving cell, different other neurotransmitter like acetyl cholinesterase break acetylcholine down so it can be reprocessed. Alzheimer's disease distorts cells that create and use acetylcholine by reducing the amount available to carry impulse. The breakdown of acetylcholine can be reduced by blocking the activity of acetyl choline esterase. Regulating the level of acetyl choline can help to make up loss functioning of brain cells.

5.7 Memantine (Inhibition of Glutamatergic Activity)

Excessive glutamatergic activity in Alzeheimer patient can be prevented by memantine. A review which is done previously showed that memantine at a dosage of 20 mg per day over six month somewhat improved cognition and ability to do activities which is needed for daily living. Memantine having brand name (Namenda) is given in order to improve memory, attention, reason, language and the capacity to do easy tasks. It was the first Alzheimer's drug of the NMDA receptor antagonist type to get recognization in United States. It prescribed to treat moderate-to-severe Alzheimer's. The FDA refused to approve memantine for mild Alzheimer's in the year 2005.

5.7.1 Mechanism of Action Memantine

The mechanism action of memantine is on regulation of the activity of glutamate which is a chemical involved in information processing, storage and regaining. Glutamate has a key role in learning and memory by enforcing NMDA receptors to allow a controlled amount of calcium into a nerve cell. The calcium enters into the nerve cell needed to create the chemical environment required for

information storage. But elevated amount of glutamate highly stimulates NMDA receptors so that they let too much calcium to enter into the nerve cells. That brings disruption and death of cells. Memantine works against excessive increase of glutamate by blocking NMDA receptors.

5.8 Selegiline (MAO type B inhibitor)

Selegiline has a minimal anticholinergic activity and it inhibit monoamine oxidase type B.

5.9 Antipsychotic (Not approved by FDA for Alzeheimer Treatment)

Antipsychotic drug is used to decrease the behavioral symptom caused by Alzeheimer disease. Anti-psychotic drug like olanzapine and risperidone lower aggression and psychosis in Alzheimer patient.

5.10 Non-pharmacological Treatment

- Diagnosis of the disease at its early stage and providing support for a patient at its initial stage of the disease.
- Giving awareness training aimed at increasing enhancing mental wellbeing.
- Regulating the patient self –sufficiency.
- Finding out a means to be free of problematic behavior
- Enhancing the way of living standard or life style for a patient associated with dementia.
- Reducing the gap of communication between the patient and physician.

6. Conclusion

Alzheimer's disease is mainly related with our genetic makeup, way of life as well as the environmental factors that affect our nerve cell can be considered as the predisposing factor. At its early stage it might be associated with losing the ability to remember things (forgetfulness) and the patient can't think clearly. The medication available now a days for treating Alzheimer's is just for a time being is just to reduce the symptom associated with it and to treat the symptom related with mental, emotional and intellectual fluctuations. Medication will not permanently reduce the symptom as well as they can't prevent the brain cell from death. Various type of service, programs will help the patient. The people mainly above the age of 65 years old can be affected by the non mendelian genetically complex type of Alzheimer's type. Now a days different study indicates show presence of different predisposing gene for late on set type of Alzheimer's disease. Finally, understanding the risky gene that cause the disease and acquiring knowledge about how is our brain cell respond for it and finding out a means to enhance cognitive function as well as reducing mood fluctuation, and mental disruption will help to reduce the disease from becoming severe.

7. Acknowledgement

I would like to express my special thanks of gratitude to my teacher "Dr. Nagaraju Bandaru" for his able guidance and support in completing my review.
I would also like to extend my gratitude to management of KL University, Guntur district.

8. Conflict of Interest

Author has declared no conflict of interest

9. References

1. Smith MA. Alzheimer disease. Int Rev Neurobiol. 1998; 42:1–54. https://doi.org/10.1016/S0074-7742(08)60607-8.
2. Cummings JL, Cole G. Alzheimer disease. JAMA. 2002; 287(18):2335–8. https://doi.org/10.1001/jama.287.18.2335. PMid:11988038.
3. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991; 82(4):239–59. https://doi.org/10.1007/BF00308809. PMid:1759558.
4. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol. 2011; 7(3):137–52. https://doi.org/10.1038/nrneurol.2011.2. PMid:21304480. PMCid:PMC3339565.
5. Cummings JL, Cole G. Alzheimer disease. JAMA. 2002; 287(18):2335–8. https://doi.org/10.1001/jama.287.18.2335. PMid:11988038.
6. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell. 2012; 148(6):1204–22. https://doi.org/10.1016/j.cell.2012.02.040. PMid:22424230. PMCid:PMC3319071.

7. Winslow BT, Onysko M, Stob CM, Hazlewood KA. Treatment of Alzheimer disease. Am Fam Physician. 2011; 83(12):1403–12.
8. Batsch NL, Mittelman MS. World Alzheimer Report 2012. Overcoming the Stigma of Dementia. Alzheimer's Disease INTERNATIONAL (ADI), London; 2012.
9. Jonsson T, *et al*. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med. 2013; 368(2):107–16.
10. Knuesel I, *et al*. Maternal immune activation and abnormal brain development across CNS disorders. Nat Rev Neurol. 2014; 10(11):643. https://doi.org/10.1038/nrneurol.2014.187. PMid:25311587.
11. Krstic D, Knuesel, I. Deciphering the mechanism underlying late-onset Alzheimer disease. Nat Rev Neurol. 2013; 9(1):25. https://doi.org/10.1038/nrneurol.2012.236. PMid:23183882.
12. Sosa-Ortiz, AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. Arch Med Res. 2012; 43(8):600–8. https://doi.org/10.1016/j.arcmed.2012.11.003. PMid:23159715.
13. Bonda DJ, *et al*. Role of metal dyshomeostasis in Alzheimer's disease. Metallomics. 2011; 3(3): 267–70. https://doi.org/10.1039/c0mt00074d. PMid:21298161. PMCid:PMC3117398.
14. Van Gorp B, Vercruysse T. Frames and counter-frames giving meaning to dementia: A framing analysis of media content. Soc Sci Med. 2012; 74(8):1274–81. https://doi.org/10.1016/j.socscimed.2011.12.045. PMid:22386639.
15. Melo A, *et al*. Oxidative stress in neurodegenerative diseases: mechanisms and therapeutic perspectives. Oxid Med Cell Longev. 2011. https://doi.org/10.1155/2011/467180. PMid:22191013. PMCid:PMC3236428.
16. Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nutr. 2000; 71(2):621S–9S. https://doi.org/10.1093/ajcn/71.2.621s. PMid:10681270.
17. Esler WP, Wolfe MS. A portrait of Alzheimer secretases--new features and familiar faces. Science. 2001; 293(5534):1449–54. https://doi.org/10.1126/science.1064638. PMid:11520976.
18. Skoog I, Kalaria RN, Breteler MM. Vascular factors and Alzheimer disease. Alzheimer Dis Assoc Disord. 1999; 13:S106–14. https://doi.org/10.1097/00002093-199912003-00016. PMid:10609689.
19. Larson EB, *et al*. Survival after initial diagnosis of Alzheimer disease. Annals of internal medicine. 2004; 140(7):501–9. https://doi.org/10.7326/0003-4819-140-7-200404060-00008. PMid:15068977.
20. Engelhart MJ, *et al*. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA. 2002; 287(24):3223–29. https://doi.org/10.1001/jama.287.24.3223. PMid:12076218.
21. De la Torre JC. Alzheimer disease as a vascular disorder: Nosological Evidence. Stroke. 2002; 33(4):1152–62. https://doi.org/10.1161/01.STR.0000014421.15948.67. PMid:11935076.
22. Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. N Engl J Med. 2013; 368(13):1169–71. https://doi.org/10.1056/NEJMp1302513. PMid:23484795.
23. Rafii MS, Aisen PS. Recent developments in Alzheimer's disease therapeutics. BMC Medicine. 2009; 7(1):1–4. https://doi.org/10.1186/1741-7015-7-7. PMid:19228370. PMCid:PMC2649159.
24. Crismon ML. Tacrine: first drug approved for Alzheimer's disease. Ann Pharmacother. 1994; 28(6):744–51. https://doi.org/10.1177/106002809402800612. PMid:7919566.
25. Mayeux R, Sano M. Treatment of Alzheimer's disease. N Engl J Med. 1999; 341(22):1670–79. https://doi.org/10.1056/NEJM199911253412207. PMid:10572156.
26. Molinuevo J L, *et al*. Current state of Alzheimer's fluid biomarkers. Acta Neuropathol. 2018; 136(6):821–53. https://doi.org/10.1007/s00401-018-1932-x. PMid:30488277. PMCid:PMC6280827.
27. Behrens S, *et al*. Use of FDA approved medications for Alzheimer's disease in mild dementia is associated with reduced informal costs of care. Int Psychogeriatr. 2018; 30(10):1499. https://doi.org/10.1017/S104161021800011X. PMid:29559029. PMCid:PMC6150839.
28. Bassil N, Thaipisuttikul P, Grossberg GT. Memantine ER, a once-daily formulation for the treatment of Alzheimer's disease. Expert Opin Pharmacother. 2010; 11(10):1765–71. https://doi.org/10.1517/14656566.2010.493874. PMid:20540654.
29. Lleo A, Greenberg SM, Growdon JH. Current pharmacotherapy for Alzheimer's disease. Annu Rev Med. 2006; 57:513–33. https://doi.org/10.1146/annurev.med.57.121304.131442. PMid:16409164.
30. Romero K, *et al*. The future is now: model-based clinical trial design for Alzheimer's disease. Clin Pharmacol Ther. 2015; 97(3):210–14. https://doi.org/10.1002/cpt.16. PMid:25669145. PMCid:PMC6463482.