ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY
Review Article

Recent Approach to Alzheimer's Syndrome and Dementia- A Review

Manju Tembhre*

M K Ponda College, Barkatullah University, Bhopal, India

***Corresponding Author**: Manju Tembhre, M K Ponda College, Barkatullah University, Bhopal, India.

Received: August 04, 2017; **Published:** September 21, 2017

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease causes depletion in memory, judgment, communication and cognitive functioning. Over the past decades AD is one of the commonly fatal diseases in the baby boomer population. The search for a treatment to Alzheimer's hasn't been going well. There are only a few approved drugs that treat symptoms of the disease these are Razadyne (galantamine), Exelon (rivastigmine), Memantine and Aricept (donepezil). In rapid aging of society, neurodegenerative diseases such as Alzheimer's disease, is widely-recognized as serious problems that need to be addressed. The objective of the present review is to provide the reader with an updated account of Alzheimer's Syndrome and Dementia and currently available biomarkers for AD and clinically relevant differential diagnoses.

Keywords: *Alzheimer's Disease; Dementia; Biomarkers for AD*

Introduction

Alzheimer's disease (AD) is a slowly progressive, age-related neurodegenerative brain disease and is the most frequent cause of the dementia syndrome in elderly. It was first identified by Alois Alzheimer in 1060 in Germany. It has become a global health concern as the population of ageing people, is growing alarmingly. It is estimated that in 2050, over 80 million people will suffer from AD worldwide and will be a major public health problem [1]. According to the recent report of Alzheimer's Association [2] the occurrence in 2017 among persons over age 65 is expected to be 5.3 million i.e. one in 10 people or 10 percent have Alzheimer's dementia in U.S. alone. Autopsy study of dementia victims in Florida found AD pathology in 77% of cases, whereas 26% had Lewy Body Disease, 18% had vascular dementia, 13% had hippocampal sclerosis, and 5% had Fronto Temporal Dementia (FTD) [3].

AD is an irreversible brain disease that slowly destroys memory and thinking skills and eventually even the ability to perform the simplest daily tasks. The main symptoms include memory loss, cognitive impairment, disorientation and psychiatric symptoms [4]. AD pathology begins even much before the arrival of clinical symptoms. Findings of the Dominantly Inherited Alzheimer's Network (DIAN) study found brain changes starting 10 to 20 years before the commencement of dementia symptoms in people genetically intended to get Alzheimer's disease [5].

Mapping Alzheimer's disease involves mainly seven stages [6]. First stage is the earliest phase of normal outward behavior with no apparent symptoms except a PET scan, an imaging can reveal whether the person has got Alzheimer's. Stage 2 - 4 show very mild, mild and moderate decline changes which include forgetting a word or misplacing objects, forgets something he just read, asks the same question repeatedly, face more trouble making plans or organizing and can't remember names of new people they meet and the problems in thinking and reasoning such as forget particulars about himself, forget what date, month or season it is and having trouble cooking meals. In the stage 5 moderately severe decline changes showing state of confusion and patient start to lose track of place and time. He develops trouble remembering general information's like his address and phone number. Stage 6 is severe decline stage with clear symptoms of confusion relating people correctly or delusions such as thinking he needs to go to work even though he has retired long back. The stage 7 is very severe decline phase, a final stage of Alzheimer's dementia in which secondary symptoms of AD e.g. depression, agitation, aggression, hallucinations, delusions,

sleep disorders appears. The life expectancy of AD patients may vary from 4 - 10 years depending on young or old age. Amalgamation of several causes has made a challenge to investigate pre-dementia diagnosis of AD. It is highly prudent to discover reliable biomarkers, to spot its exact pathophysiology during pre-symptomatic stage. Biomarker(s) with high sensitivity and specificity would facilitate AD diagnosis at early stages. Currently, CSF amyloid β 1-42, total tau, and phosphorylated tau181 are used as AD biomarkers [7].

Despite the increase in aging population affected with AD and its distressing way, and the huge social and economic costs, current treatments are only symptomatic and marginally effective. Recent research in AD focuses mainly on the synthesis drugs that can reverse or slow the advancement of AD and target to beta-amyloid production, aggregation, and clearance, as well as tau phosphorylation and assembly. But up till now none of these drugs have exhibited promising results in III phase of clinical trial [8]. Toward the discovery of such agents, the multi-pronged of mechanisms of its onset must be understood and to formulate appropriate therapies for effective prevention or treatment.

Key Factors of AD: There may be several factors of onset of AD depending on the person's physiological setup.

CSF Beta Amyloid (Aß): The major cause leading to AD appears to be the formation of a peptide (protein) known as amyloid beta (beta amyloid, Aß) which clusters into amyloid plaques (senile plaques) on the blood vessels and on the outside surface of neurons of the brain (amyloidosis), which ultimately leads to the killing of neurons. The major constituents of amyloid plaques, are the β-amyloid peptides consisting of 40 and 42 amino acids (Aβ1-40 and Aβ1-42), which are derived from the amyloid precursor protein (APP) present in different cell membranes [9]. There are two enzymes alpha-secretase (α-secretase) and beta-secretase (β-secretase or BACE1 - with the identification of the gene that produces it, beta-secretase has been renamed BACE (Beta-site APP-Cleaving Enzyme) that initially compete to cut APP. If alpha-secretase cuts APP there is no formation of Aß. If APP is cleaved by beta-secretase it can then be further cleaved by gamma-secretase (γ-secretase) to form either a 40 amino acid amyloid peptide ($Aß_{40}$) which is soluble and mostly harmless - or a 42 amino acid peptide ($Aß_{42}$) which clusters together to form insoluble amyloid plaques [10]. Beta peptide ($Aß_{42}$) is more hydrophobic and "sticky" (and hence aggregates more readily) than the ($Aß_{40}$). Alpha-secretase cleavage takes place at the cell surface, whereas beta-secretase acts at the endoplasmic reticulum. Gamma-secretase produces $Aß_{42}$ if cleavage occurs in the endoplasmic reticulum, however $Aß_{40}$ is formed if the cleavage is in the trans-Golgi network [11]. The β-amyloids become folded in the β-folded or β-pleated shape, and then pile on each other to form long fibrils and aggregates known as plaques in AD patients [12]. The combination of decreased concentrations of Aβ1-42 (or Aβ1-42/Aβ1-40 ratio) and increased concentrations of total tau and P-tau in cerebrospinal fluid (CSF) are also considered to be indicator of stages of Alzheimer's disease [13]. Treatment strategies include inhibitors of β- and γ-secretase, to prevent aggregation of the amyloids [14]. A number of immune strategies and a cholesterol-decreasing approach are also being assessed to get rid of the β-amyloids.

CSF Tau Protein: Alzheimer's is characterized by massive loss of neurons and disrupted signaling between cells in the brain. One of the important causes of dementia is the involvement of Tau proteins, which aggregate together to form neuronal tangles in the brain of AD patient. In healthy person the Tau protein is connected to microtubules of cytoskeleton of the nerve cell and supports the cell structure. In AD patients' tau is displaced from the cytoskeleton in the nerve cells and eventually tangles collectively to form protein accumulations that interrupt the nerve cell's functioning. Actually tau proteins become hyper-phosphorylated and lose the capacity to bind to microtubules. Instead, the phosphorylated tau proteins bind to each other, tying themselves in "knots" (paired helical filaments - two threads of tau wound around each other) known as NeuroFibrillary Tangles (NFTs). Neurons full of NFTs rather than functional microtubules soon die. These NeuroFibrillary Tangles (NFT's) are made up of paired helical filaments consisting of hyperphosphorylated tau protein (P-tau). Tau protein itself is an intracellular protein that is released upon neuronal death. As clumps or tangles advances the risk of patient's death rises. If tau is prevented from locking onto the vesicles in the nerve cells in AD patient's brain, will prevent inhibition of synaptic transmission and also the death of nerve cells [15]. This protein may offer an opportunity for therapeutic intervention. Studies are ongoing with agents that may prevent or reverse excess tau phosphorylation and thereby diminish formation of neurofibrillary tangles.

Cholinesterase Inhibition: Over last five decades it was commonly accepted that Alzheimer's disease (AD) is a lack of the acetylcholine (ACh) in the brain and it has been demonstrated that the inconsistent shortage of neurotransmitter acetylcholine leads to Alzheimer's disease [16]. It is well established that acetylcholinetransferase and acetylcholinesterase accountable for acetylcholine synthesis and its degradation are declined in the neocortex and hippocampus areas of the brain involved in cognition and memory [17]. Further, density of nicotinic acetylcholine receptors in the cerebral cortex decreases in AD patients. Muscarinic Acetylcholine receptors play an important role in learning & memory. Over three-quarters of cholinergic neurons in the basal forebrain nuclei are seen to be destroyed in a typical AD autopsy. Loss of choline acetyltransferase in the nucleus basalis was the first biomarker of AD. Centrally acting ChE inhibitors (ChEI) prevent the breakdown of acetylcholine. At present few such agents have been approved by the FDA for the treatment of AD, which are Donepezil, Rivastigmine and Galantamine. Rivastigmine and galantamine inhibit butyrylcholinesterase as well as AChE. Galantamine has a direct stimulant action upon nicotinic receptors. Nausea, vomiting and diarrhea are the most common side effects of the AChE inhibitors. Approximately 50% of AD patients treated with AChE inhibitor show lack of cognitive deterioration for up to two years [18].

Genetic Factors: Tau-protein encoding gene is located on chromosome 17 and is considered not responsible for any Familial AD (FAD). It is the PS1 (Pre-Senilin **1**) gene located on chromosome 14 accounts more for FAD. PS1 is the main enzyme cleaving the gamma-secretase site. PS1 is present within the endoplasmic reticulum/Golgi complex. Abnormal proteins from the PS1 and PS2 genes apparently influence gamma-secretase enzyme causing more $Aß_{42}$ peptide formation [19]. Numerous lines of evidence suggest that one of the best known genetic key risk factor for Alzheimer's disease in men or women is a gene that carries instructions for a protein called apolipoprotein E (APOE4) which transport cholesterol and beta-amyloid in and out of cells. The mutations on chromosome 19 to the APOE gene are described as a "risk factor" for Sporadic AD. APOE gene occurs in three common forms (alleles): APOE2, APOE3 and APOE4. Each person has two copies of chromosome 19, therefore there are 6 combinations of the 3 alleles when taken 2 at a time (e2/e2, e2/e3, e2/e4, e3/e3, e3/e4 and e4/e4). The APOE4 allele increases amyloid deposition on blood vessel walls, the APOE2 allele increases the likelihood of a lobar intra-cerebral hemorrhage [19]. A new study by researchers at the Stanford University School of Medicine reveals that carrying just one copy of the ApoE4 gene results in a two to four times greater risk of Alzheimer's disease on women than it does on men. Inheriting two copies increases the risk nearly 10 - 15 times [20]. It is still to confirm that why AD is much more prevalent in women than in men for any given age group, but some evidence suggests that it may be due to an interface between the APOE-e4 genotype and the sex hormone estrogen [21]. Studies have shown that estrogen replacement treatment in post-menopausal women can increase cerebral blood flow and improve cognitive performance. On the other hand the brains of men bear the capacity to alter testosterone to estrogen with advancing age, which may explain the greater prevalence of AD among women [22]. The greater longevity also contributes for women's increased susceptibility to Alzheimer's. Some studies have suggested that lower educational attainment in women than in men could be a possible reason for a higher risk of Alzheimer's and other dementias in women [23]. The TOMMORROW trial is enrolling people with a genetically-based increased risk of AD determined through the use of a pharmacogenetic algorithm based on TOMM40 and APOE genotype and age [24]. In Down's syndrome victims the mutation on chromosome 21 (the chromosome that is present in triplicate in Down's syndrome) is on the Amyloid Precursor Protein (APP) gene itself, resulting in abnormal APP protein that is preferentially cleaved by secretases to form more $Aß_{42}$. Hence Down's syndrome patients may develop AD by the age of 40 [19].

Biomarkers of AD: Early diagnosis of AD is difficult because early symptoms of the disease are common in a variety of disorders, which reflects general neuropathological features. Conventional diagnosis of AD was based on combination of clinical criteria which includes a neurological examination, mental status tests and brain imaging [25]. But these tests prove to be difficult especially in patients having mild or early stages of AD. There is immense necessity of specific, easy-to-use and responsive biomarkers to distinguish AD from other types of dementia, such as mild cognitive impairment (MCI), or mixed forms of dementia, such as fronto temporal lobe dementia (FTLD), vascular dementia (VaD) or Lewy body dementia (LBD). This is imperative because therapy for these diseases may be different [26,27].

Currently, dementia is diagnosed by analyzing Cerebrospinal Fluid (CSF) with valid biomarkers like β-amyloid (1-42) [Aβ(1-42)], total tau protein and phospho-tau 181expression levels. Decreased CSF concentration of the amyloid- β (1-42) peptide (Aβ) and an increased

level of the protein tau are found in patients with AD [28]. These biomarkers considerably enhance the validity for diagnosis by giving > 95% sensitive and > 85% specific results [29,30]. It has been demonstrated that Amyloid beta is an efficient, highly sensitive and specific biomarker from CSF for AD. Recent researches have shown that Semi-quantitative amyloid PET appears more powerful than CSF markers for AD grading and MCI prognosis in terms of cognitive decline and AD conversion [31].

The analysis of other 199, -231, -235, -396 and -404 forms of phosphorylated tau in CSF might offer indication to early diagnosis of AD [32]. Phospho-tau-231 and phospho-tau-181 are more specific to differentiate AD from controls and FTLD, LBD, VaD and major depression [33]. Increased levels of P-tau have been reported with AD patients compared with patients having FTD and VAD, DLB and Parkinson disease with dementia. P-tau shows 92 and 64% difference with specificities between patients with AD and patients with FTD and DLB respectively [34].

According to findings of Alexopoulos *et al*. [35] on MCI patients with positive $A\beta_{42}$ values are at the same risk for AD dementia whether or not they have one positive Tau marker (either t-Tau or p-Tau). Hence, patients with positive $A\beta_{42}$ and non-positive or conflicting p-Tau/t-Tau levels, is not who cannot be categorized according to the current NIA-AA (National Institute on Aging/Alzheimer's Association) algorithm, appears under the same dementia risk, which occurs between that of the lowest and highest risk groups.

Recent Research on AD: New studies are focusing on evaluating Aβ as a potential biomarker from blood serum as well. This might help recognize the disease earlier because of the simple method and high frequency of blood collection [36]. Obtaining blood samples is relatively painless and inexpensive, giving potential blood-based biomarkers further advantage over the CSF-based markers. More importantly, efforts are warranted to mine newer biomarkers to prevent AD and dementia and are to search such diagnostic strategy which could be utilized as a prescreening tool to predict cerebral Aβ deposition or other factors lead to AD.

Recent evidence suggests the progressive loss of brain cells seen in Alzheimer's disease (AD) may be due to brain cells taking up and releasing specific aggregated proteins (misfolded proteins, which clump together). Recently Scientists have reported that the suppression of expression of synapse-restricting protein Ephexin5 restores Alzheimer's-like impairment in mice [37].

Scientists' have identified a new gene PTPRD (Protein Tyrosine Phosphatase, Receptor type D) gene that is associated with Tau accumulation in the brain. This accumulation occurs in Alzheimer's disease and certain forms of dementia [38].

Recently a gene called USP9 (Ubiquitin Specific Peptidase 9) is identified that is much more active in the brains of healthy women than in men with AD. This gene has an indirect influence on the tau protein, which is found in higher levels in the AD brain. In addition, they noticed that blocking the USP9 gene significantly reduced the tau activity [39].

AXON Neuroscience, a global leading Biotech Company in development of tau immunotherapies has found promising results from its Phase I trial for the vaccine AADvac1. AADvac1 is an active immunotherapy directed against tau protein, the main constituent of neurofibrillary tangles. Further researches are going on to find safe, correct and targeted therapy of AD.

Conclusion

There is soaring need to discover a potentially new way to get Alzheimer's medications, a long-standing challenge that could help clear the brain of the build-up of the toxic protein known as amyloid beta (AB) and other factors that leads to Alzheimer's. Still AD treatment awaits breakthrough, which may take a lot of time for a potential treatment for Alzheimer's disease to work its way from the laboratory, through rigorous testing and, finally, to become approved by the U.S. Food and Drug Administration (FDA).

Bibliography

1. Schneider JA., *et al*. "The neuropathology of probable Alzheimer disease and mild cognitive impairment". *Annals of Neurology* 66.2 (2009): 200-208.

2. Alzheimer's Association. "Alzheimer's Disease Facts and Figures". *Alzheimer's and Dementia* 13.7 (2017): 325-373.

3. Barker WW. "Relative Frequencies of Alzheimer Disease, Lewy Body, Vascular and Frontotemporal Dementia, and Hippocampal Sclerosis in the State of Florida Brain Bank". *Alzheimer Disease and Associated Disorders* 16.4 (2002): 203-212.

4. Kumar P., *et al*. "Circulating miRNA biomarkers for Alzheimer's disease". *PLoS One* 8.7 (2013): e69807.

5. Sperling RA., *et al*. "Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease". *Alzheimer's and Dementia* 7.3 (2011): 280-292.

6. Ward A., *et al*. "Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: A systematic review of the literature". *Dementia and Geriatric Cognitive Disorders Extra* 3.1 (2013): 320-332.

7. Sharma S and Lipincott W. "Biomarkers in Alzheimer's Disease-Recent Update". *Current Alzheimer Research* (2017).

8. Salomone S., *et al*. "New pharmacological strategies for treatment of Alzheimer's disease: focus on disease-modifying drugs". *British Journal of Clinical Pharmacology* 73.4 (2011): 504-517.

9. Tapiola T., *et al*. "Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain". *Archives of Neurology* 66.3 (2009): 382-389.

10. Lathia JD., *et al*. "Notch: From Neural Development to Neurological Disorders". *Journal of Neurochemistry* 107.6 (2008): 1471-1481.

11. Hartmann T., *et al*. "Distinct sites of intracellular production for Alzheimer's disease A beta40/42 amyloid peptides". *Nature Medicine* 3.9 (1997): 1016-1020.

12. Choi SR., *et al*. "Correlation of amyloid PET ligand florbetapir F 18 binding with Aß aggregation and neuritic plaque deposition in postmortem brain tissue". *Alzheimer Disease and Associated Disorders* 26.1 (2012): 8-16.

13. Albert MS., *et al*. "The diagnosis of mild cognitive impairment 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 and Dementia* 7.3 (2011): 270-279.

14. Seeman P and Seeman N. "Alzheimer's disease: β-amyloid plaque formation in human brain". *Synapse* 65.12 (2011): 1289-1297.

15. Pritchard SM., *et al*. "The toxicity of tau in Alzheimer disease: turnover, targets and potential therapeutics". *Journal of Cellular and Molecular Medicine* 15.8 (2011): 1621-1635.

16. Francis PT., *et al*. "The cholinergic hypothesis of Alzheimer's disease: A review of progress". *Journal of Neurology, Neurosurgery, and Psychiatry* 66.2 (1999): 137-147.

17. Livingston G and Katona C. "How useful are cholinesterase inhibitors in the treatment of Alzheimer's disease? A number needed to treat analysis". *International Journal of Geriatric Psychiatry* 15.3 (2000): 203-207.

18. Bullock R. "New drug for Alzhiemer's Disease and other Dementia's". *British Journal of Psychiatry* 180 (2002): 135-139.

19. Brouwers HB., *et al*. "Apolipoprotein E Genotype Is Associated With CT Angiography Spot Sign in Lobar Intracerebral Hemorrhage". *Stroke* 43.8 (2012): 2120-2125.

20. Altmann A., *et al*. "Sex modifies the APOE-related risk of developing Alzheimer disease". *Annals of Neurology* 75.4 (2014): 563-573.

21. Yaffe K., *et al*. "Estrogen use, APOE, and cognitive decline: Evidence of gene-environment interaction". *Neurology* 54.10 (2000): 1949-1954.

22. Birge SJ. "Is there a role for estrogen replacement therapy in the prevention and treatment of dementia?" *Journal of the American Geriatrics Society* 44.7 (1996): 865-870.

23. Rocca WA., *et al*. "Sex and gender differences in the causes of dementia: A narrative review". *Maturitas* 79.2 (2014): 196-201.

24. Roses AD., *et al*. "A pharmacogenetic-supported clinical trial to delay onset of mild cognitive impairment (MCI) due to Alzheimer's disease". Poster #34249. Alzheimer's Association International Conference Vancouver, Canada (2012).

25. Barthel H., *et al*. "Cerebral amyloid-β PET with florbetaben (18 F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study". *The Lancet Neurology* 10.5 (2011): 424-435.

26. Sjögren. "Advances in the detection of Alzheimer's disease-use of cerebrospinal fluid biomarkers". *Clinica Chimica Acta* 332.1-2 (2003): 1-10.

27. Desai AK. "Diagnosis and treatment of Alzheimer's disease". *Neurology* 64.3 (2005): S34-S39.

28. Shaw LM., *et al*. "Cerebrospinal fluid biomarker signature in Alzheimer's Disease Neuroimaging Initiative subjects". *Annals of Neurology* 65.4 (2009): 403-413.

29. Marksteiner J., *et al*. "Cerebrospinal fluid biomarkers for diagnosis of Alzheimer's disease: Beta-amyloid (l-42), tau, phospho-tau-181 and total protein". *Drugs of Today* 43.6 (2007): 423-431.

30. Blennow K., *et al*. "Cerebrospinal fluid and plasma biomarkers in Alzheimer disease". *Nature Reviews Neurology* 6.3 (2010): 131-144.

31. Bouallègue FB., *et al*. "Comparison of CSF markers and semi-quantitative amyloid PET in Alzheimer's disease diagnosis and in cognitive impairment prognosis using the ADNI-2 database". *Alzheimer's Research and Therapy* 9 (2017): 32.

32. Blennow K. "CSF biomarkers for Alzheimer's disease: use in early diagnosis and evaluation of drug treatment". *Expert Review of Molecular Diagnostics* 5.5 (2005): 661-672.

33. Hampel H. "Total and phosphorylated tau protein as biological markers of Alzheimer's disease". *Experimental Gerontology* 45.1 (2010): 30-40.

34. Hall S., *et al*. "Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders". *Archives of Neurology* 69.11 (2012): 1445-1452.

35. Alexopoulos P., *et al*. "Conflicting cerebrospinal fluid biomarkers and progression to dementia due to Alzheimer's disease". *Alzheimer's Research and Therapy* 8 (2016): 51.

36. Park JC., *et al*. "Chemically treated plasma Aβ is a potential blood-based biomarker for screening cerebral amyloid deposition". *Alzheimer's Research and Therapy* 9 (2017): 20.

37. Gabrielle L Sell., *et al*. "Reducing expression of synapse-restricting protein Ephexin5 ameliorates Alzheimer's-like impairment in mice". *The Journal of Clinical Investigation* 125.5 (2017): 1646-1650.

38. Chibnik LB., *et al*. "Susceptibility to neurofibrillary tangles: role of the PTPRD locus and limited pleiotropy with other neuropathologies". *Molecular Psychiatry* (2017).

39. Köglsberger S., *et al*. "Gender-Specific Expression of Ubiquitin-Specific Peptidase 9 Modulates Tau Expression and Phosphorylation: Possible Implications for Tauopathies". *Molecular Neurobiology* (2016).

Volume 4 Issue 5 September 2017