International Journal of Basic Medical Sciences and Pharmacy (IJBMSP)
Vol. 5, No. 2, December 2015, ISSN: 2049-4963

www.ijbmsp.org

Alzheimer's disease, Epidemiology, causes, diagnosis and novel treatments: A review.

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Abstract – This review reveals current innovations in pathology, diagnosis and novel treatment options for Alzheimer's disease. Alzheimer's disease (AD) is a progressive neurodegenerative disorder named after Alois Alzheimer, who first described this disorder more than one century ago. It is the most common cause of dementia, accounting for up to 75% of all dementia cases. There are two major pathological hallmarks of the AD, extracellular plaques containing various forms of amyloid-β protein (Aβ), and intracellular neurofibrillary tangles (NFTs), composed of hyper-phosphorylated tau protein. Mutations and polymorphisms in multiple genes (Presenilin 1, presenilin 2 genes and Apo lipoprotein E) contribute to familial and sporadic forms of AD. There is no accurate diagnostic method; the only method of definitively diagnosing AD is a brain autopsy. However, medical history, neuropsychological testing, and neuroimaging techniques allow physicians to make an accurate diagnosis of AD. Apart from traditional therapies (antioxidants, Acetyl cholinesterase inhibitors, and NMDA receptor antagonists) this review also exposes modern treatments options for AD (immunotherapy, cell transplantation and gene therapy).

Keywords – Alzheimer's disease; tau protein; Oxidative Stress; Acetylcholinesterase inhibitors; Immunotherapy; secretase inhibitors.

1. Introduction

Alzheimer's disease (AD) is a progressive, permanent neuronal syndrome that take place progressively and consequences in memory loss, unusual behavior personality changes, and loss of the ability to thinking [1]. Alzheimer's disease was first recognized by a German physician, Dr. Alois Alzheimer in 1907 who described a group of pathologic defects in the brain of a 51 year old woman "Auguste Deter" who was affected by memory problems, misunderstanding and language malfunctions. He stated that there are some dense plaques external the neurons and neurofibrillary tangles (NFT) or groups of fibers internal the brain cells associated with inflammation, oxidative stress, and nerve cell death while he was examining the autopsy of Auguste Deter's brain. Afterward other characteristics of the disease were described by Emil Kraepelin [2]. Plaques comprised of amyloid beta (Aβ) often known as amyloid plaques, and NFT contains hyperphosphorylated tau protein [3]. These two have been recognised to be the basic of Alzheimer's diseases.

1.1. Epidemiology

Alzheimer's disease (AD) is the most common type of dementia; accounts for an estimated 50-75% percent of cases [4]. Worldwide 35 million people affected by AD. In 2050, the incidence of AD is expected to approach nearly a million people per year, with a total estimated prevalence of 11 to 16 million people in the USA. AD is more common in female as compare to male. More than 60 percent of Alzheimer's and dementia caregivers are women. Almost two-thirds of Americans with Alzheimer's disease are women. Alzheimer's disease is the sixth leading cause of death in the United States [5]. The frequency of Alzheimer's disease multiplies with age, doubling every five to ten years. Its ratio in different age groups are 1% (65-69 years), 3% (70-74 years), 6% (75-79 years), 12% (80-84 years), and 25% (85 years and above) [6].

1.2. Symptoms of AD

The most common initial symptom of Alzheimer's is the consequence of breakdown and destruction of neuronal channels in brain cells

The following are common symptoms of AD:

Loss of memory, Problems with words in speaking or writing, Difficulty to carry out everyday jobs, Planning or solving problems, Confusion with time or place, Trouble with understanding images, Changes in mood and personality (anger, anxiety, and depression) and Difficulty in in talking and understanding [7] [8].

1.3. Pathophysiology of AD

Alzheimer's is a multi-factorial disease and the exact causes of AD are not clear, a complex mechanisms underlying the pathogenesis of memory impairment in AD are oxidative stress theory, gene mutations theory, cholinergic hypothesis, β-amyloid theory, Tau protein hypothesis, Age, Psychosocial hypothesis (i.e. Education socioeconomic status, Social network and social engagement, Physical activity, mental activity), Other etiologic hypotheses (inflammation, toxic exposure, and other factors) Anti-Inflammatory Drugs, Head Trauma, Vascular pathway

hypothesis (e.g. smoking, obesity, and high total cholesterol) and vascular morbidity (e.g. high blood pressure, diabetes, and silent brain infarcts and white matter lesions), Nutritional and dietary factors, Cerebral and cardiovascular disease, Environmental causes (e.g., head trauma, viruses, toxins, low education level) [9].

Less than 5% of all AD cases are caused by gene mutation.

1.4. Causes of Alzheimer's disease

1.4.1. Genetic

Scientists have found evidence of a link between Alzheimer's disease and genes mostly on four chromosomes, labeled as 1, 14, 21, and 19 [10].

1.4.2. Early onset and Early-onset Familial AD (EOFAD)

Early onset represents only a small fraction of all AD cases (≤5%) and typically presents with onset ages younger than 65 years, almost 13% seeming to be inherited in an autosomal-dominant manner mutations of Down syndrome, one extra copy of chromosome (trisomy 21) in affected families [11]. FAD makes up less than 1% of all cases of Alzheimer's mostly at 40s [12]. To date, in 3 genes have been reported to cause EOFAD. These include the Aβ precursor protein (APP) on chromosome 21 (21q21.3), presenilin 1 (PSEN1) on chromosome 14 (14q24.3), and presenilin 2 (PSEN2) on chromosome 1 (1q31-q42)

Early-onset familial Alzheimer disease (EOFAD): molecular genetics [13] as shown as in below table.

Locus name	Proportion of EOFAD	Gene symbol	Chromosomal locus	Protein name	Mutations
AD3	20–70%	PSEN1	14q24.3	Presenilin-1	155
AD1	10–15%	APP	21q21	Amyloid beta A4 protein	23
AD4	Rare	PSEN2	1q31-q42	Presenilin-2	9

Most mutations in the APP and presenilin genes increase the production of a small protein called Aβ42 and Aβ40, which is the main source of neuronal cell death and dementia [14]. APP is cleaved by a membrane-bound protein complex called γ-secretase to generate Aβ. Presenilins 1 and 2 are the enzymatic centers of this complex along with nicastrin, Aph1, and PEN-2. Alpha-secretase cleavage of APP, which precludes the production of Aβ, is the most common processing event for APP. Presenilin 1 acts together with glycogen synthase kinase (GSK3b) and causes increased hyperphosphorylation of tau protein [15].

1.4.3. Late onset or sporadic AD

It is the most common about 90 percent of those afflicted with Alzheimer's suffer from the late onset form which is typically diagnosed at the age of 65 or older. A gene found on chromosome 19 (19q13.2-13.3) known as APOE has been proven to affect the likelihood of developing Alzheimer's. On chromosome 19, the apolipoprotein E (APOE) gene has three common forms or alleles: e2, e3, and e4. Thus, the possible combinations in one person are e2/2, e2/3, e2/4, e3/3, e3/4, or e4/4. ApoE gene on chromosome 19 involved in making ApoE, a ApoE is essential for a normal metabolism of lipoproteins, cholesterol and triacylglycerols. The APOE e4 gene is considered a "risk factor" gene for AD and appears to influence the age of onset of the disease [16].

1.4.4. Amyloid-β Protein

Amyloid beta Aβ (first described by Glenner and Wong (1984) is derived from the amyloid- protein precursor (AβPP) via complex proteolytic pathway catalyzed by a number of secretases [17]. The principal component of amyloid is the β-amyloid protein (Aβ), a ~4-kDa of 39-43 amino acid peptide composed of a 11-15 amino acids of the transmembrane domain and 28 amino acids of the extracellular domain of amyloid precursor protein (APP) and is the main component of amyloid plaques found in Alzheimer's patients [18]. Under normal conditions amyloid precursor protein (APP) proteolysis is obtained by the proteolytic enzymes α-, β- and γ-secretase and generates non-amyloidogenic fragments. Aβ protein is generated by successive action of the β and γ secretases. Mutations in the APP gene on chromosome 21q21 encompassing -400 kb of DNA , and the presenilins (PS-1, PS-2) account for most of the familial early onset cases of AD by enhancing the production of pathological Aβ -40 or 42 amino acid form. Presenilins 1 gene on chromosome 14q24.3 and 2 gene on chromosome 1q31-q42 are multitransmembrane proteins that, associated to nicastin, APH-1 and PEN-2, form high molecular α -secretase complex, involved in Aβ production through the intramembrane cleavage of AβPP [19-20]. The mechanism by which amyloid beta may damage and kill neurons is not fully understood, a variety of studies suggest that Aβ may have toxic properties, particularly in the aggregated state by generating reactive oxygen species and destabilize lysosomal membranes, resulting in cell death .When this occurs on the membrane of neurons it causes lipid peroxidation and the generation of a toxic aldehyde called 4-hydroxynonenal which, in turn, impairs the function of ion-motive ATPases, glucose transporters and glutamate transporters. As a result of amyloid beta promotes depolarization of the synaptic membrane, excessive calcium influx and mitochondrial impairment [21].

1.4.5. Phosphorylated Tau Protein

Tau is an extremely soluble Microtubule-Associated Proteins (MAPs), it is comparatively abundant in neurons but is present in all nucleated cells and functions physiologically to bind microtubules and stabilize microtubule assembly for polymerization. These functions of tau are regulated by its degree of phosphorylation. The human tau gene is located over 100 kb on the long arm of chromosome 17 at band position 17q21 and contains 16

exons [22]. A normal level of phosphorylation is required for the optimal function of tau, whereas the abnormally hyperphosphorylation of tau, particularly that mediated by MARK (microtubule-affinity-regulating kinase), CDK5 (cyclin-dependent kinase 5) and GSK3β (glycogen synthase kinase 3β), destabilizes microtubules, causing impairments in axonal transport and neuronal dysfunction. Self-assembly of hyperphosphorylated tau results in the formation of Neurofibrillary Tangles (NFTs) [23]. Tau protein has more than 40 known phosphorylation sites and becomes hyperphosphorylated in NFTs in AD neurons with some sites being only phosphorylated in the AD – specific soluble form of tau protein termed paired helical filaments (PHF) - tau in AD. Normal brain tau contains 2-3 moles of phosphate per mole tau, but Tau mutations result either in increase in 4-repeat: 3-repeat tau ratio higher than that of the normal human brains or in missense mutations in the protein of autopsied AD brain [24]. The pathology of tau is much similar to Aβ. Tau considered toxic due to its insolubility, Tau protein loses its capacity to bind to microtubules thus makes NFTs .The tau intracellular overexpression or mislocalization may destabilized the plus-and minus end-directed transport of vesicles . Inhibition of transport to the plus-end of microtubule slows down exocytosis and affects the distribution of mitochondria which become clustered near to the MTOC. The absence of mitochondria and endoplasmic reticulum in the peripheral regions of the axons could produce a decrease in glucose and lipid metabolism and ATP synthesis and loss of Ca2+ homeostasis that leads to a distal degeneration process referred to as “dying back” of axons [25].

1.4.6. Oxidative Stress

In humans the brain, as a relatively small organ mass, has a disproportionately high level of oxygen consumption due to its high ATP demand. It consumes about 20% of the body’s total basal oxygen and subsequently generates relatively high level of ROS [26]. The link between AD and OS (oxidative stress) is additionally supported by the finding of decreased levels of antioxidant enzymes, increased protein, lipid and DNA oxidation and advanced glycation end products (AGEs) and ROS formation in neurons of AD patients [27]. Evidence suggests that ß-amyloid may directly disrupt mitochondria function and contribute to the deficiency of energy metabolism and neuronal death seen in AD. The presence of A-beta in mitochondria was associated with impaired mitochondrial metabolism and increased mitochondrial ROS production [28]. Mitochondrial dysfunction due to ROS together with reduced NADH-ubiquinone oxidoreductase might play an important role in tau pathology. There is evidence that disruption of zinc homeostasis may play an important role in microtubule and tau pathology. Zinc and iron can bind tau and promote aggregation and phosphorylation [29]. On the other hand, oxidative stress may act on genes influencing their activity. Thus, some genes, like the E4 allele gene on chromosome 19, can be stimulated in the context of increased oxidative stress, leading to increased expression of E apolipoprotein, with negative effects on neuronal plasticity processes, such as learning and memory, which are, of course, seriously affected in Alzheimer's disease [30].

1.4.7. Cholinergic Hypothesis

The cholinergic hypothesis was firstly proposed by Sims et al in 1981. They proposed that the synthesis of acetylcholine, a neurotransmitter, was low in the neocortex of the brain in AD patients. In supporting this concept, the level of cholineacetyl transferase was clearly found down regulated up to 80-90% in the hippocampus and temporal cortex and up to 40-75% in the parietal and frontal cortex, and cholinergic neuron counts in the nucleus basalis was generally lowered in AD condition. In post-mortem studies, the enzyme cholineacetyltransferase has been found to be diminished in brains of AD patients . It has been show that β-amyloid reduces choline uptake and Ach release in vitro. Cholinergic system also influences Tau phosphorylation. The reduced activity of cholinergic neurons in AD may therefore lead to a reduced activation of phospholipase C, increased GSK-3 activity, and consequently to hyperphosphorylation of tau proteins [31].

1.4.8. The Theory of Glutamate Neurotoxicity/Calcium Hypothesis

The theory of glutamate neurotoxicity and the calcium (Ca2+) hypothesis belong to the same theory. Simpson et al found that glutamate-containing nerve terminals are severely reduced in AD. Glutamate can increase the intracellular Ca2+ activity. This finally leads to a Ca2+ influx via NMDA receptor of glutamate, an excitatory amino acid, which can act on the NMDA receptors on spinal cord neurons, channels and results in dysregulation of multiple Ca2+-dependent processes including learning or memory loss. Based on this observation, the calcium hypothesis was suggested, and antagonist of NMDA receptor was being investigated for its application as a novel therapeutic approach for AD [32-33].

1.5. Diagnostic Screens and Tests of AD

The early diagnosis of AD is very important because treatment at the initial stage of this disease reduces its progression and delays the hospitalization of the patient as long as possible. There is no accurate diagnostic method; the only method of definitively diagnosing AD is a brain autopsy. However, mental and behavioral tests and physical examinations allow physicians to make an accurate diagnosis of AD in 90 percent of cases [34].

1.5.1. Medical History

The first step in finding a diagnosis is obtaining the patient history. During this time, the physician will determine what symptoms are present, when they began, and how they have progressed over time. The family history of illness is also pertinent.

1.5.2. Neuropsychological Testing

The physician will examine the cognitive functioning, identifies behaviors and behavioral changes, and measures performance in comparison with other persons of the same age.

Abnormal performance can be determined only by

comparison with a normal control group matched for age, sex, and local education.Different others tests like Mini-Mental State Examination' for cognitive screening, the Blessed Dementia Scale' for clinical symptoms and social function, the Hamilton Depression Scale for severity of depression, the Present State Examination for anxiety, depression, delusions, and hallucinations and the Hachinski Scale for estimating the likelihood of multi-infarct dementia are performed [35].

1.5.3. Laboratory Tests

Thyroid function tests may reveal hypothyroidism, which can be associated with depression, irritability, and slowing of mental processes. Vitamin B12 deficiency may produce psychiatric symptoms and myelopathy, with or without neuropathy, and may occur in the absence of hematopoietic abnormalities. Tests for sexually transmitted disease or human immunodeficiency virus, which can also produce psychiatric symptoms along with dementia, should be included only for patients who appear to be at specific risk for this etiology [36].

1.5.4. Neuroimaging Techniques

1.5.4.1. PET

Positron emission tomography (PET) has been used to study the brain's metabolic uptake of fluorine 18 (18F)-labeled fluorodeoxyglucose (FDG) and blood flow in patients with dementia. Positron emission tomography (PET) uses radiation signals to create a three-dimensional color image of the human body. The patient is injected (18F)-labeled fluorodeoxyglucose (FDG) which travels to the organs that use that specific molecule for energy. As the compound is metabolized, positrons are emitted. The energy from these positrons is detected by the PET scan, which converts the input to an image. This image reflects the function of the patient's body by showing how effectively the radiotracer is broken down. The amount of positron energy emitted creates a variety of colors and intensities, which reflects the extent of brain activity. A PET scan has the capacity to detect changes in metabolism, blood flow, and cellular communication processes in the brain [37]. In addition another radiolabeled agent ^{11}C labeled 6-hydroxy-2-(4'-N-[^{11}C] methylaminophenyl-1, 3-benzothiazole, also known as Pittsburg compound B (^{11}C-PIB), being used to bind with cerebrovascualr amyloid deposits [38].

1.5.4.2. Computerized Tomography (CT)

The technique can define gyri and sulci and quantitate tissue densities, ventricular size, CSF volume, and brain mass. In Alzheimer's disease, the volume of the ventricular system and the width of the third ventricle are increased, gyri are narrowed, and sulci are widened; however, these general patterns may not be particularly useful as diagnostic criteria in individual cases [39].

1.5.4.3. Magnetic Resonance Imaging (NMR)

The proton nuclear magnetic resonance (NMR) image, or magnetic resonance imaging (MRI), reveals the differentiation of gray and white matter of the brain and has therefore proved useful in studies of demyelinating disorders. The ^{125}I labeled Aβ40 (^{125}I-Aβ40) and gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA), have high binding affinity to the amyloid plaques in human and double transgenic AD mouse and provided T2 contrast that corresponded with the signal on T1 spin echo [40].

1.5.4.4. Single Photon Emission Computerized Tomography (SPECT)

Cerebral SPECT, which is based on brain uptake of a technetium 99m–based lipid-soluble radionuclide such as ethyl cysteinate dimer or hexamethylpropylene amine oxime, is a widely available technique for evaluation of brain perfusion with a rotating gamma camera [41].

1.5.4.5. Genetic Markers

Genetic testing can be performed by using numerous markers. Mutations of the *PS-1*, *PS-2*, and amyloid precursor protein genes on chromosomes 1, 14, and 21, respectively, are associated with early onset of the familial and extremely rare form of AD. The only useful marker for the more common late-onset (sporadic form) dementia is the apolipoprotein APOE ε4 allele on chromosome 19 among the other two isoforms is associated with a high incidence of AD, whereas the ε2 allele may be a protective factor. The ε3 allele is thought to represent no increased or decreased risk .The ε4 allele is found in about 30% of healthy subjects and is absent in approximately 30%–40% of patients with AD [42]. The Oxidative stress biomarkers i.e. lipid peroxidation, protein oxidation, DNA oxidation, superoxide dismutase, and glutathione system are used to find out the Oxidative stress, a pathophysiologic imbalance between oxidants and antioxidants in favor of the former, with potential damage, has been shown in the blood, cerebrospinal fluid (CSF), and brain of neurologic patients with probable AD [43].

1.6. Treatment Strategies

1.6.1. Cholinergis

Acetylcholinesterase inhibitors (AChEIs) inhibit the action of acetylcholinesterase (AChE) enzyme that breaks down the neurotransmitter acetylcholine, a chemical messenger help to deliver messages to other cell. Alzheimer's disease damage or destroys cells that produce and use acetylcholine, thereby reducing the amount available to carry messages. A cholinesterase inhibitor slows the breakdown of acetylcholine by blocking the activity of acetylcholinesterase. By maintaining acetylcholine levels, the drug may help compensate for the loss of functioning brain cells [44] Four AChEI are approved by US Food and Drug Administration (FDA) for AD. They are Donepezil (trade name Aricept® , Eisai Company and Pfizer Inc.) , Galantamine (Hoechst Marion Roussel Inc., Shire Pharmaceutical Group, and Janssen Pharmaceutical, trade names Reminyl® and Nivalin, U.S. trade name Razadyne®), Tacrine (trade name Cognex®), and rivastigmine (trade name Exelon®, Novartis Pharmaceuticals) [45].

1.6.2. N-methyl-D-aspartate receptor (NMDA) Antagonists

In 2003, the FDA approved Memantine (Namenda; Forest Laboratories, New York, NY), a low to moderate-affinity noncompetitive NMDA receptor antagonist, for the treatment of moderate to severe AD. In 2005, the FDA declined to approve memantine for mild Alzheimer's. Memantine appears to work by regulating the activity of glutamate, a chemical involved in information processing, storage and retrieval. Glutamate plays an essential role in learning and memory by triggering helps create the chemical environment required for information storage. Excess glutamate, on the other hand, overstimulates NMDA receptors so that they allow too much calcium into nerve cells. That leads to disruption and death of cells. Memantine may protect cells against excess glutamate by partially blocking NMDA receptors [46].

1.6.3. Antioxidant Therapy

Antioxidant therapy, as one of the promising therapeutic strategies for AD, has been studied for years. Antioxidants are substances, which can work by different ways, stop or slow down the formation of free radicals, scavenge or neutralize free radicals by absorbing the single unpaired electron, thereby turning it into a less reactive species thus prevent damage to neurons [47].

1.6.4. Dietary Antioxidants

The most widely studied dietary antioxidants are vitamin C, vitamin E, vitamin B12, omega-3 polyunsaturated fatty acid (docosahexaenoic acid) caffeine, curry spice curcumin, and vitamine A (β-carotene) [48]. Vitamin C is considered the most important water-soluble antioxidant in extracellular fluids, as it is capable of neutralizing ROS in the aqueous phase before lipid peroxidation is initiated. It was demonstrated that persons with a higher intake of vitamin C (ascorbic acid) had a reduced risk of developing AD, compared to those with lower intake [49]. Vitamin E (α-tocopherol) is a major lipid-soluble antioxidant, and is the most effective chain breaking antioxidant within the cell membrane, where it protects membrane fatty acids from lipid peroxidation, reduced Aβ levels and senile plaque deposition, and decreased F2-IsoPs levels in AD [50]. Various dietary supplements such as omega-3 polyunsaturated fatty acid (docosahexaenoic acid), Caffeine (500 mg or 5-6 cups of coffee a day) , epigallocatechin-gallate esters from green tea curry spice curcumin and red wine (Cabernet Sauvignon) have been shown to inhibit amyloidosis and Aβ production in both cell culture and animal models [51].

1.6.5. Traditional Herbal Antioxidants Drugs

Ginkgo biloba contains compounds that have antioxidant and anti-inflammatory properties that protect neuron membranes, regulate neurotransmitters, and retard cell degeneration.

In vitro data show that Ginkgo biloba extract EGb 761 reduces βA and neuron death. European study showed equal efficacy between Ginkgo biloba (240 mg daily), Donepezil (5 or 10 mg daily) and a combination of the two [52].

1.6.6. Enzymatic Antioxidant

Superoxide dismutase (Mn/Cu/ZnSOD), catalase, glutathione peroxidase and Peroxiredoxins are enzymes involved in direct elimination of active oxygen species (superoxide radical and H2O2) in Alzheimer's.

Mitochondrial antioxidant enzyme i.e. MnSOD, lipases, proteases, and DNA repair enzymes have shown a protective role during AD development, and MnSOD eficiency increases Aβ levels and accelerates the onset of behavioral alteration in APP transgenic mice. In addition, glutathione reductase, glucose-6-phosphate dehydrogenase, and cytosolic GST are secondary enzymes that function to decrease peroxide levels or to maintain a steady supply of metabolic intermediates like glutathione (GSH) and NADPH for optimum functioning of the primary antioxidant enzymes [53].

1.6.7. Mitochondria-Targeted Antioxidants (MTAs)

Mitochondrial-related pathways are required to break the main sources of ROS. Nicotinamide adenine dinucleotide (NADH), α-lipoic acid (LA), coenzyme Q10 (ubiquinone), Mito Q, Szeto Schiller (SS) peptide, and glutathione are effective antioxidants against ROS. ALA(α-lipoic acid), also called thioctic acid, as a powerful antioxidant therapeutic and the coenzyme of mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, can recycle other antioxidants such as vitamins C and E and glutathione and increase the production of acetylcholine or as a chelator of redox-active metals to combat the accumulation of lipid peroxidation products , CoQ10 (ubiquinone) is a potent antioxidant and also an important cofactor of the electron transport chain where it accepts electrons from complex I and II. It preserves mitochondrial membrane potential during oxidative stress and protects neuronal cells through attenuating Aβ overproduction and intracellular Aβ plaque deposits. Co-enzyme Q10 and nicotinamide adenine dinucleotide (NADH) are needed for the generation of ATP by mitochondria, so it is essential to use these antioxidants for AD prevention. Mito Q is produced by conjugation of the lipophilic triphenylphosphonium (TPP+) cation to coenzyme Q With help of TPP+, coenzyme Q penetrates into the membrane core and reaches the mitochondrial matrix where it is reduced to its active form (the antioxidant ubiquinol) by complex II to decrease lipid peroxidation, resulting in reduced oxidative damage. Szeto Schiller (SS) peptide SS31 and SS20 prevented the neurotoxin 1-methyl-4-phenylpyridium (MPP+-) induced inhibition of oxygen consumption and ATP production and mitochondrial swelling to decreases mitochondrial toxicity [54].

1.6.8. Hormones

Both Estrogens and Melatonin (N-acetyl-5-methoxytryptamine) hormones occurring naturally and are powerful antioxidants.. Merlo et al. reported that estrogen can activate matrix metalloproteinases-2 and −9 to increase beta amyloid degradation and offer mitochondrial support, protects against tau tangles, and reduces βA

toxicity. Melatonin (N-acetyl-5-methoxytryptamine) is a tryptophan metabolite, synthesized mainly by the pineal gland [55].

1.6.9. Immunotherapy

Immunotherapy is in initial stages in AD patients. Recent studies of both active (vaccination) and passive (monoclonal antibodies) shows βA decreased treated with AN1792/QS-21and showed increased T-cell activation. Both Wyeth and Elan worked on both passive immunization Bapineuzumab i.e Aβ peptide antibody (AAB-001) and active immunization (ACC-001) and hoped to be effective while avoiding potential side effects by inducing a highly specific antibody response to Aβ (NCT00479557) [56].

1.6.10. Secretase Inhibitors

Research reveals that plasma βA can possibly reduce by the two inhibitors i.e. gamma and Beta-secretase. The γ-secretase inhibitors DAPT were studied in mice/rats for the treatment of AD and resulted resulted in decreased Aβ levels in plasma and cerebrospinal fluid (CSF). Beta-secretase inhibitors i.e. Memoquin also inhibits AChE, reduces βA production and decrease the tau hyperphosphorylation in animals [57].

2. Conclusion

We concluded that the current progressive rate of AD can mark a million people per year by 2050, without proper diagnostic techniques and treatment is start that brakes the drive of the disease. Current therapies provide little relief to AD, but are not the proper solution of the disease. In the future we need advance earlier detection methods and treatment to make possible to prevent or delay Alzheimer's disease.

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