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Review Article

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Pathology and Management of Alzheimer's disease: A review

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ABSTRACT

Dementia is a progressive disorder associated with neuronal loss, cognitive impairment and different levels of synaptic damage. These changes are not only complex but also very dynamic as aging progresses. Dementia is irreversible when caused by disease or injury but may be reversible when caused by drugs, alcohol, hormone or vitamin imbalances or depression. There are over 50 causes of dementia such as vascular dementia (VD), alcohol-related dementia, Huntington's disease (HD), Lewy body dementia (LDB), Parkinson's disease, Pick's disease, multisystem atrophy and motor neuron disease. The most common type which accounts for 50 to 70 percent of all people with dementia is Alzheimer's disease (AD). AD is a neurodegenerative disorder characterized by slow, progressive memory loss due to gradual loss of brain cells (neurons). This disorder affects intellectual functions such as language, cognition, attention, visuospatial perception and judgment. The incidence of AD increases with age. This disorder affects about 3% of 65 to 74 year-olds, 19% of 75 to 85 year-olds and 47% of 85 and above. The indicative symptoms rarely appear before the age of 50. So far, not one single factor has been identified to account for AD directly. It is believed that AD results from one or a combination of age, genetic factors, environmental factors and other physiological changes i.e., inflammation. This review discusses the Pathology and Management of Alzheimer's disease.

Keywords: *Dementia, Alzheimer's Disease, Neurofibrillary Tangles (NFT), Brain-Derived Neurotrophic Factor (BDNF), Parkinson's Disease*

INTRODUCTION

Alzheimer's disease (AD) was first described in 1906 by a German physician named Dr Alois Alzheimer [1]. A post-mortem analysis of the brain of his 51-year-old patient revealed extensive senile plaques and neurofibrillary tangles (NFT) formation. There are two stages of AD. People at an early onset (FAD-familial form of AD) may experience confusion, lapses of short-term memory loss, mood swings, and they are more withdrawn. FAD is a very rare form of the disease that can occur in the people between the ages of 30-60. This is known to be entirely inherited. The neuropathological characteristic of late-onset (sporadic form) is similar to the early stage but more severe. This usually develops after the age of 60.

It can be difficult to differentiate between the different types of dementia using laboratory tests only, as not all of the causes of dementia can be identified. Neuroimaging (Structural and Functional**)** has been widely used to help in the diagnosis of dementia [2].

Morphology

Patients with AD show several degrees of atrophy in cortical regions associated with cerebral nuclei widening that appear commonly in the frontal, parietal and temporal lobes (Figure 1,2). Also, there is dilation of cerebral ventricles indicating the loss of parenchyma [3]. Other neuromorphological changes include thinning of the cortical gyri, widening of the sulci, and enlarging of the ventricles which translates (microscopically) to a loss of grey matter.

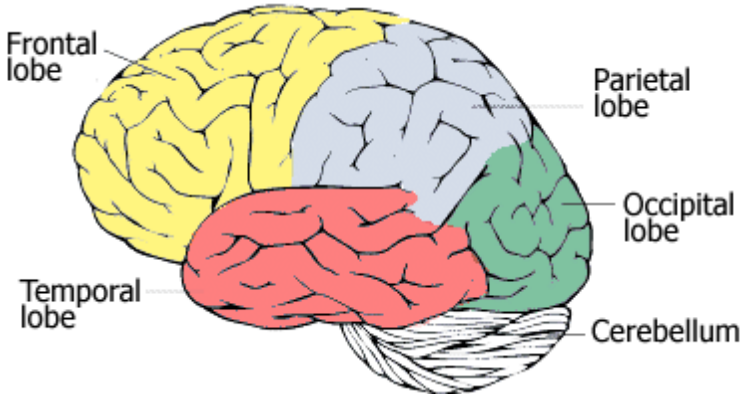


Figure 1. The brain

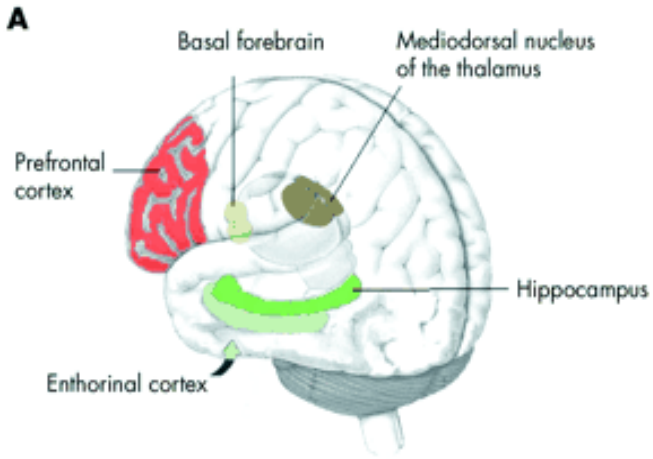


Figure 2. A more detailed picture of the brain

Neuropathology

The AD is characterized by NFT and neuritic/sensile plaques (B-amyloid plaques), cholinergic cell loss and general brain shrinkage [4]. Tangles are composed of paired helical filaments known as NFT (figure 3). They contain an aberrant hyperphosphorylated fibrillary protein known as tau which is a microtubule-associated protein that enhances microtubule assembly [5]. These tangles are present in the cytoplasm of neurons which are mainly located in the cerebral cortex, especially in the entorhinal cortex and also in the pyramidal cells of the hippocampus, amygdala, basal forebrain and raphe nuclei [3]. NFTs in the hippocampus and the basal forebrain can lead to impaired learning, and they may also cause a deficit in cholinergic neurotransmitters such as acetylcholine (ACh). Tangles disturb the cytoskeleton also disrupting cell structure causing impairments in axonal transport and synaptic viability leading to neuronal dysfunction [5].

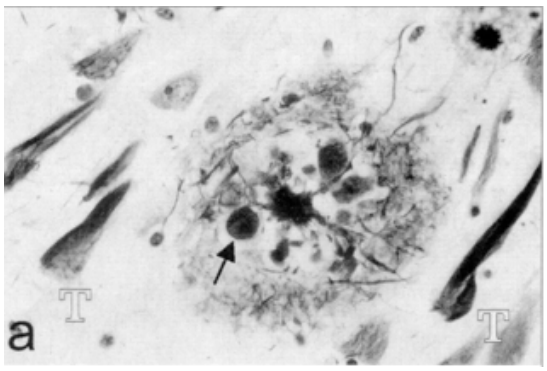


Figure 3. Neurofibrillary Tangles (letter T) and senile plaque in the centre [6]

B-A myeloid Plaques commonly referred as neuritic plaques or senile plaques (Figure 4) are extracellular deposits of β-Amyloid Protein (Aβ) having a central core of Aβ surrounded by numerous abnormal axons and degenerating

mitochondria. The most abundant component of the plaque core is Aβ, a peptide of approximately 40-43 amino acids. Apolipoprotein (ApoE) is also present in the core of plaque but to a lesser extent. These plaques have a variable size ranging from 20 to 200μm and are found particularly in the neocortex, hippocampus, and amygdala [3].

Aβ is cleaved from a large precursor protein amyloid (APP). Mutation in APP gene leads to the familial forms of early-onset of AD which generated the amyloid cascade hypothesis.

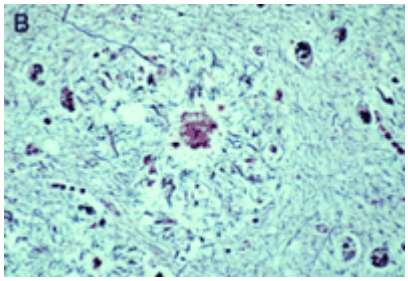


Figure 4: Amyloid plaque in Amygdala [7]

Molecular biology

APP (which produces β-Amyloid) is a protein (of 695 amino acids) with a domain, found on the long arm of chromosome 21. From in vitro experiments, it was suggested that it is a single transmembrane protein and is thought to have the following potential functions: cell adhesion molecule, aid to neurite outgrowth and synaptogenesis and a promoter of cell survival. It has been suggested that AD is not due to Aβ formation but to the cleavage of APP [8]. In all of the eight known mutations, a single mutation in the gene for APP can produce the full neuropathological and symptom profile of AD.

In normal situations, APP is cleaved by enzyme α-secretase between 16 and 17 residues forming a large soluble fragment which is not neurotoxic and a smaller anchored fragment that is cleaved by a γ-secretase enzyme [9]. However, this cleavage does not give rise to Aβ fragments (figure 5). This pathway is present in the cell membrane. The APP is cleaved by enzymes β-secretase and γ-secretase, respectively, resulting in the formation of less soluble Aβ fragments (Aβ 40 and Aβ 42 are the most common) [8] which are neurotoxic, this cleavage has been shown to exist inside lysosomes (Figure 5).

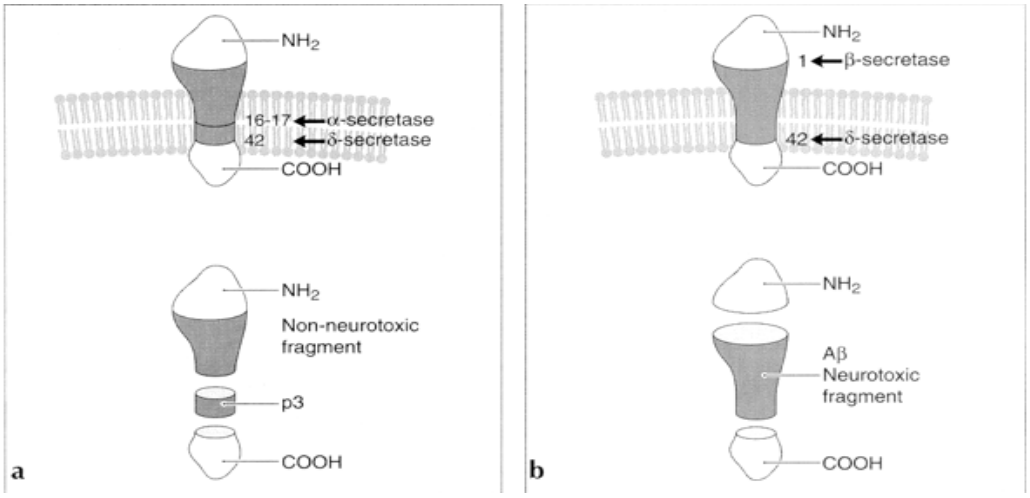


Figure 5. Structure of APP (a) cleavage of APP via α secretase (b) cleavage of APP via β secretase

Two genes have been found on chromosome 14 & 1 which encode for two intracellular proteins, presenilin (PS) 1 and PS 2 [3]. In the neuronal cell bodies the interaction between the PS and β APP is critical for organizing vesicular traffic, but when interrupted there is impairment of the delivery of synaptic vesicles to the presynaptic terminals. PS 1 mutations account for up to 50% of a FAD, and PS 2 mutations are also responsible for the AD, but these are rare. These mutations are thought to increase the production of Aβ-42, as it affects the APP activity [8].

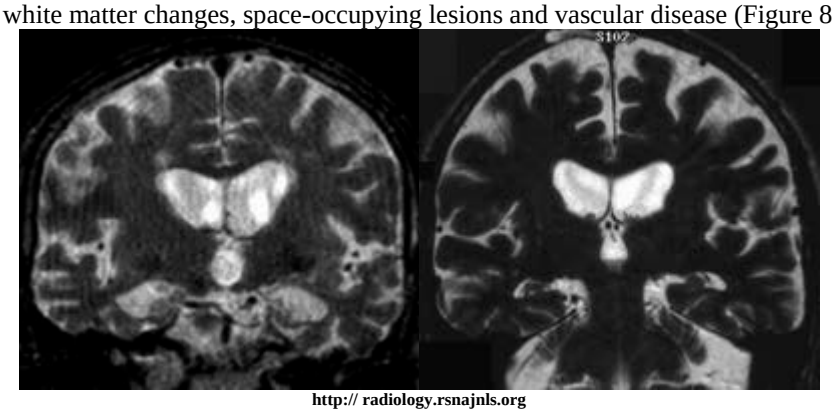
ApoE mutation is considered as a major risk factor for the development of AD [10]. ApoE is a lipid transport molecule, a constituent of very low-density lipoproteins (VLDL) and a subclass of high-density lipoproteins (HDL). This lipoprotein plays an essential role in the maintenance of the neuronal structure, cholinergic function, and synaptic

repair. Lipoproteins are also responsible for carrying cholesterol and other fats through the bloodstream and are essential for the normal breakdown of these molecules. ApoE acts as a scavenger for Aβ and also forms a complex with it, transporting it from the brain into the bloodstream.
The ApoE gene is positioned on chromosome 19 in band 19q13.2, in which it presents in 3 allelic forms ε2, ε3, and ε4. ApoE ε2, a rarely occurring form, may provide some protection, ApoE ε 3, the most common form, appears to play a neutral role. ApoE ε 4 is found in 40 percent of people with AD, and this form increases the risk of AD by 5 to 15 fold [11]. Having this gene form does not mean that a person will develop AD, but people who inherit two copies of the ε4 allele have a higher chance of developing AD.

Diagnosis assessment
Diagnosis of the AD is using pathologic examinations of tissue derived from an autopsy or a brain biopsy [12]. In living subjects, diagnosis is made by using clinical, laboratory and imaging assessment for evidence of possible AD. Neurological examinations are also used to help assess cognitive dysfunction. These include MMSE (mini-mental state Exam, IPR (Immediate paragraph recall) and DFR (Delayed figure recall). Clinical scores of these neurological examinations relate to the supposition of NFT and amyloid plaques. Individuals with higher NFT or amyloid density would perform poorly on clinical tests [13].

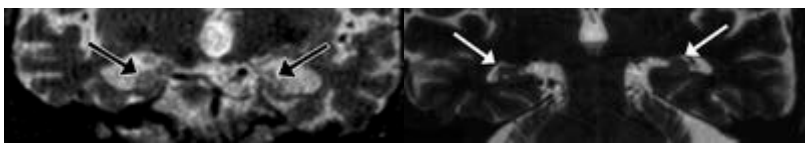
Neuroimaging assessment
Structural imaging (MRI and CT) provides an image of the brain, differentiating types of tissue by recognizing ischemic changes and/ or patterns of atrophy which point towards a particular cause of dementia (Figure 6 and 7). Functional imaging measures neural activity indirectly using glucose metabolism or cerebral blood flow as surrogate markers hence indicating the presence of a degenerative disease. Modalities include PET, SPECT, MRI.
CT (Computerised tomography) involves an X-ray beam rotating around the head and measuring shrinking of the brain [8]. Differentiation of normal grey and white matter and visualization of gyral-sulcal patterns can be observed using this scan [14].

Functional MRI (f-MRI) - The MR dataset can give a display of the density of hydrogen nuclei (common referred to as proton density), slice by slice through the brain. The mobility of the protons within a particular tissue is what gives rise to the MR signal [8]. Both CT and MRI used to measure degree of atrophy of the hippocampus and entorhinal cortex in the brain, white matter changes, space-occupying lesions and vascular disease (Figure 8 and 9) [15].



http:// radiology.rsnajnls.org

Figure 6,7. MRI images in patient with AD (left) showing atrophy in the Hippocampus, compared to MRI image of a normal patient (right)



Figures 8,9. MRI images in AD patient (left) showing severe bilateral hippocampal atrophy (arrows) indicating intensity of atrophy compared to a normal person's absence of hippocampus perfusion (right) [16]

PET is used to determine glucose metabolism and CBF (cerebral blood flow) by radioactive tracers which emit positrons that collide with an electron to produce γ rays. The PET converts these γ rays into visible photons, used to construct a 3D image. Two different techniques of PET are used ^{18}F-FDG (18F-fluorodeoxyglucose) enables cerebral glucose metabolism to be established after intravenous injection of radio-labeled glucose. In a study of regional metabolic activity with FDG-PET, a decrease of frontal task-related activation (during a verbal memory task) with increasing age was found [8, 17].

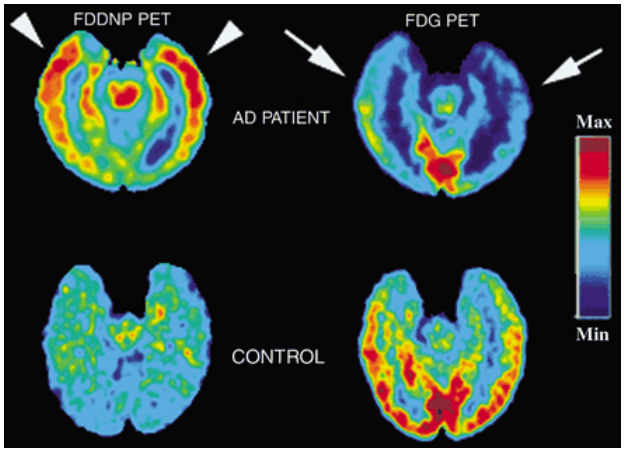


Figure 10. FDG and [^{18}F] FDDNP - PET images detecting glucose metabolism in a patient with AD (above) and a control subject (below) indicating temporal deficits shown by arrows in patients with AD in contrast to normal subjects [15]

$^{15}O_2$ oxygen PET involves inhalation of ^{15}O-labelled oxygen or infusion of ^{15}O-labelled water. Both methods quantify absolute values for metabolism and CSF from the images (Figure 10) [8]. It is sensitive in assessing the physiological parameters such as receptor binding and has a high resolution.
SPECT- involves the detection of γ rays produced by radioactive tracers. Absolute quantification of regional CBF and perfusion is obtained using the ^{133}-Xenon inhalation technique. Both PET and SPECT generate three-dimensional images of brain function [18].

fMRI utilizes the magnetic properties of oxygenated and deoxygenated blood to estimate CBF, with a high intensity indicating a high level of blood oxygenation. The fMRI tracks neural activity by detecting changes in blood flow during resting and cognitive tasks [19]. Using MRI, it has been possible to study different areas of medial temporal lobe such as hippocampus, parahippocampal gyrus, subiculum, entorhinal cortex, and amygdala [2]

Neuroimaging of non – alzheimer's disease
There is no difference in the atrophy of frontal lobe, temporal lobe and ventricular volumes between AD and VD [19], but patients with VD display hippocampal atrophy which is less marked than AD but is more distinct in patients with Lewy body dementia (DLB). Frontal variants of frontotemporal dementia (FTD) [2] were indistinguishable from AD, whereas the presence of asymmetrical degeneration of the frontal and anterior temporal lobes in FTD distinguishes it from the AD [8]. The pattern of hypometabolism is quite different in FTD, as compared with AD. FTD cases have a significant reduction in the glucose metabolism in the fronto and anterior temporal lobes, basal ganglia and thalamus compared to normal people. Although visual hallucinations are a typical feature of DLB, no differences in volume of occipital lobes between patients with DLB, AD and controls were found [19]. A diagnosis of vascular dementia is supported by the presence of relevant vascular changes in either CT or MRI. In vascular Dementia white matter changes are extensive, and irregular. The absence of vascular changes excludes VD.

It is difficult to distinguish between AD and DLB, using structural imaging due to overlapping features (Dawbarn and Allen, 2001) [8]. Considerable overlap of patterns is also seen in patients with Creutzfeld-Jacob disease (CJD), and Parkinson's disease with dementia. CJD scans show non-specific atrophy. Therefore, CT is insensitive to changes in CJD as movement artifacts cause a major problem.

Imaging in alzheimer's disease
Cortical atrophy, reduced brain weight and ventricular enlargement are all more outstanding in AD patients compared to normal people. This is illustrated in the following figure 11. [17].

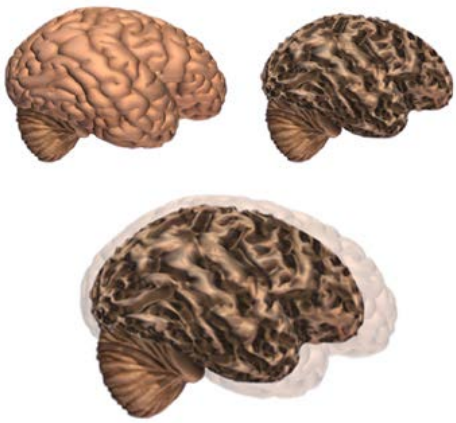


Figure 11. A picture comparing the shrinkage of the brain of a healthy person and that of a patient with AD in the right [17]

As a general rule, the pattern of bilateral temporoparietal hypoperfusion or hypometabolism provides good discrimination of AD patients not only from age-matched normal controls, but also from VD or frontal lobe dementia (FLD) patients. AD is characterized by impairment of temporoparietal regional glucose metabolism (rCMRglu) and regional cerebral blood flow (rCBF). Pseudo-dementia caused by depression may be differentiated from AD by the involvement of the frontal, amygdala and cingulate regions [17]. 100% sensitivity has been found for medial temporal lobe atrophy in AD compared with controls, but the specificity of atrophy between AD, VD and DLB patients is found to be low. However, routine use of measuring medial temporal lobe atrophy for diagnosis of AD is time-consuming in the clinical setting [19].

Hippocampal volume reduction on MRI with reduced blood flow in posterior parietotemporal cortex with SPECT has been found in AD. PET and SPECT studies have shown a reduction of oxygen metabolism in parietal and temporal cortices of patients with AD [19]. Both PET and SPECT have been used in patient screening to quantify the loss of cholinergic receptors in AD and the effect of different drugs. The uptake of radioligand by muscarinic or nicotinic acetylcholinergic receptors is shown to be low in AD patients compared to normal [9].

Neurochemistry

AD is usually linked to low levels of neurotransmitters such as serotonin, noradrenaline, dopamine and especially Ach [20]. It is believed that reduced levels of ACh can attribute directly to cell loss in the basal nuclei, temporal and parietal neocortex and hippocampus. Low levels of noradrenaline result in neuronal loss in the locus coeruleus. Reduced serotonin levels relate to NFT and neuronal loss in the dorsal raphe nucleus.

Cholinergic neurons in the Nucleus basalis, Medial septal nucleus and diagonal band of Broca that provide the principal cholinergic pathway to the neocortex and hippocampus are destroyed reducing the level of neurotransmitters such as ACh. ACh is an essential neurotransmitter required for the normal functions of the brain. Reduced levels of ACh cause neuronal loss.

Acetylcholine is degraded in the brain by two cholinesterase's acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) and synthesized by CHAT enzyme [21]. AChE is the main enzyme involved in the breakdown of ACh in normal brain, but as AD progresses, BuChE becomes increasingly involved. AD is characterized by presence of neuritic amyloid plaques and NFT which are associated with cholinergic degeneration. Blocking of cholinesterase induced hydrolysis of ACh and the subsequent increase in ACh concentration in central synapses and enhancement of cholinergic function is the most effective therapy for patients with AD.

Reactive oxygen species (ROS)

The generation of ROS, as part of the normal cellular function, is under tight homeostatic control. Oxidative stress is when ROS levels exceed the antioxidant capacity of a cell, leading to the destruction of cellular components including lipids, protein, DNA, and ultimately cell death via apoptosis or necrosis [22]. DNA oxidation, protein oxidation, and lipid peroxidation have been noticed in regions containing NFT and senile plaques of AD patients' brains [23].

Neurons are enormously sensitive to attacks by destructive free radicals. It has been reported that oxygen free radicals play a crucial role in promoting amyloid aggregation [24], but the toxicity can be eliminated by free radical scavengers

such as vitamin E, selegiline, Ginkgo biloba and ApoE [25]. Free radical scavengers have produced promising results in relation to AD [26]

Inflammation

Most organs of our body including the brain have their own inflammatory and innate immune response. While these responses are intended to deal with injury and infection, these can also be autodestructive to the neurons. The inflammatory system becomes activated once the brain acquires AD. Some of the studies have shown that anti-inflammatory drugs can reduce the prevalence of AD.

Brain-derived neurotrophic factors

Brain-derived neurotrophic factor (BDNF) is a member of neurotrophins which plays a role in survival and maintenance of the neurons in the central nervous system [27]. They are produced by neurons in hippocampus and cortex. It has been found that BDNF promotes the survival of cholinergic neurons present in the basal forebrain thereby enhancing the release of ACh which is important for normal cognitive function. BDNF binds to tyrosine kinase receptors at presynaptic and postsynaptic sites forming BDNF-TrkB complex, which plays a vital role in the survival of neurons [27].

BDNF regulates the plasticity of the neurons by enhancing transmission of synapse and excitation of neurons [28,29]. An in vivo study in mice with impaired BDNF TrkB signalling by genetic means lead to disturbances in learning and memory; these effects were reversed when BDNF was restored [30-32]. Postmortem brain of an AD patient showed low expression of BDNF and TrkB receptor supporting the involvement of BDNF in neuronal survival [33].

Treatment

- **Cholinesterase Inhibitors**:

In 1970, researchers found reduced levels of ACh in the brain of patients suffering from AD [34]. This has been supported when reduced cholinergic neurons and reduced levels of CHAT enzyme were observed in patients suffering from AD. [35]. In a study, cholinergic antagonist drugs such as Scopolamine retarded the ability to learn, and this effect was reversed by cholinergic agonist which supports the importance of ACh in cognitive function [35].

To improve cholinergic transmission, several strategies have been undertaken including: increasing synthesis of ACh, enhancing ACh release from presynapse and prevention of degradation of ACh by using cholinesterase inhibitors (ChEIs). ChEIs are the only drugs authorized by the U.S Food and Drug Administration to enhance ACh transmission because the limited evidence supports the use of other agents with similar effects to improve cognition associated with AD [36]. Tacrine was the first centrally acting ChEIs, but serious adverse effects like hepatotoxicity have limited its use [37]. Currently, three ChEIs are used to treat mild to the moderate AD which are Donepezil, Rivastigmine, and Galantamine. According to various studies, none of these drugs have shown a beneficial effect in advanced stages of AD [38, 25]. Donepezil and Galantamine are selective inhibitors to AChE, whereas Rivastigmine inhibits both AChE and BuChE.

Glutamatergic drugs

Glutamate is a neurotransmitter, being present in excess which may result in neuronal damage. It activates N-methyl-D-aspartate receptors (NMDA) present postsynaptically causing excitotoxicity which can affect memory processes. Memantine is a non –competitive inhibitor of inotropic glutamate NMDA receptor, which blocks glutamate-induced neurotoxicity. Also, it has been shown that memantine increases the expression of mRNA levels of neurotrophins in different sites of the brain [39]. Interestingly memantine was able to increase the endogenous production of BDNF; these findings suggested that memantine has neuroprotective properties.

Memantine is voltage–dependent with low to moderate affinity. It blocks the NMDA receptors in a fast on /off kinetic way, preventing the effect caused by excessive amounts of glutamate at the same time preserving the physiological activation of glutamate receptors when required [40]. Recent studies suggest that memantine could be used to treat AD because it has the ability to prevent the toxicity associated with Aβ by reducing its production [40].

Vitamin E (Alpha-tocopherol)

Vitamin E is an antioxidant, which reduces the inflammatory effects produced by plaque formation. An *in vitro* study showed that vitamin E protects nerve cells from Aβ, but it does not protect against other CNS disease caused by oxidative stress [38]. In a transgenic mouse model of AD, it has been found that vitamin E can reduce the level of peroxidase and prevent deposition of amyloid [41].

Selegiline

It is a monoamine oxidase inhibitor that stimulates the adrenergic system facilitating the release of catecholamines that play a central role in the improvement of cognitive dysfunction associated with AD. Nowadays selegiline is not widely used to treat AD because of its side effects [42] such as rigidity, agitation, and elevation of temperature when taken with meperidine.

- **Hormone -replacement therapy**

Several studies showed that postmenopausal women taking estrogen have a lower incidence in developing an AD, proposing that estrogen has a neuroprotective effect in the brain. Also, estrogen has the ability to enhance the expression of BDNF during adulthood in different parts of the brain especially forebrain [43-46] which can maintain the structure and function of neurons. However, estrogen and progestin taken together may contribute to dementia and stroke [25].

- **Anti-inflammatory agents**

It was suggested that AD represents a chronic inflammatory disease, this was supported when the brain of a patient with AD showed a large number of cytokines, chemokines, and presence of microglia and reactive astrocytes. There was evidence that people taking NSAIDs are 50% less susceptible to developing AD compared to those not receiving NSAIDs [47]. It has been suggested that NSAIDs inhibit the synthesis of prostaglandin, which in turn will reduce the transmission of the neurotransmitter glutamate that usually produces neuronal damage due to its excitotoxic effects. Some studies showed that NSAIDs such as (Ibuprofen) were able to reduce the formation of amyloid-β42 [48] by altering the activity of γ secretase. NSAID intake is usually associated with some side effects such as ulceration, renal problem and stroke. Some studies do not recommend NSAIDs in the treatment of AD as no beneficial effects have been observed [25].

- **Anti-amyloids therapy**

The aim of such treatment is to design compounds able to cross the blood-brain barrier and decrease the activity of both β and γ secretase since both enzymes produce Aβ with neurotoxic effects. These compounds could be an innovative therapy to treat early stages of the disease [49]. Few compounds that act as β secretase inhibitors were screened compared to γ secretase inhibitors, suggesting that only a few compounds can block the activity of β secretase. However, when the crystal structure of β secretase has been identified [50], it should provide a starting point for designing compounds able to prevent the activity of secretase providing new therapy in the future. Another suggestion to prevent the toxicity produced by Aβ is to create molecules able to bind with Aβ monomer preventing its aggregation to form oligomers. This could be a good target for the pathologic unit.

Cannabinoids

Cannabinoids may play a role in the treatment of AD in the future. It has been found that cannabinoids have a neuroprotective effect by blocking the stimulation of microglia and astrocytes. A study was conducted [51], in which PC12 cells were exposed to β-amyloid peptide resulting in neuronal damage, this effect was blocked by prior treatment with cannabidiol which acts by decreasing the production of ROS and lipid peroxidase leading to cell survival. Also, cannabinoids were able to enhance the expression of BDNF in different regions of the brain [52].

Gamma-aminobutyric acid antagonists (GABA)

Current clinical trials have shown that GABA antagonist could be an effective therapy in future for patients with the AD. These drugs enhance the expression of BDNF in frontal cortex and hippocampus. A double-blind study (phase II) was conducted by administering SGS742 (GABA antagonist) in 110 patients with the AD and showed an improvement in attention and cognitive function [53].

Phosphodiesterase inhibitors

Further drugs which can be used to treat AD are ones which enhance neurotrophin production by regulating intracellular messengers such as cAMP [54].

Lithium

Lithium salts are usually used for various CNS disorders. However, recent data showed that lithium was able to prevent the formation of hyperphosphorylated tau caused by aggregation of Aβ. Also, it has been investigated that these salts prevented cell death induced by Aβ in cerebellar granule and PC12 cells [55]. Lithium salts also play an essential role in enhancing the expression of BDNF.

Lipid-lowering drugs

Increased levels of cholesterol in plasma have been concerned as risk factors for AD because ApoE is found to be mutated in AD. Statins are compounds that inhibit HMG-CoA reductase, a key enzyme in the synthesis of cholesterol; they decrease the development of AD by inducing nitric oxide synthase and reducing endothelin-1 [56].
It has been found using *in vitro* studies that cholesterol favors the formation of Aβ in the brain [57,58].
In cultured cells, Statins showed an inhibitory effect on Aβ production by reducing the activity of β and γ secretase thereby enhancing the activity of α secretase. Statins are also found to have additional properties such as antioxidant, anti-inflammatory, and antiplatelet effects. Atorvastatin, also used in AD, belongs to a group of statins and is commonly prescribed to lower high cholesterol levels.

Immunotherapy
Immunization results in the production of antibodies which attack the harmful agent, using the body's own defenses to remove the xenobiotics. Immunotherapy in AD aims to inhibit secretase activity by creating monoclonal antibodies which bind to Aβ (β-amyloid) and prevent their accumulation.

In an earlier immunization study, 6 percent of the subjects developed acute meningoencephalitis, most likely caused by autoimmune T-cell activation, which resulted in cancellation of the trial. The development of vaccine targeting specific epitopes with minimal T cell activation, retaining the production of Aβ-antibodies might result in safer treatment.

Ginkgo Biloba
It has been found that patients receiving this dried extract showed no worsening in their cognitive function suggesting that this extract may have an antioxidant property.

European studies proposed that Ginkgo can enhance transmission by activating presynaptic receptors, therefore, reducing the impairment of cognitive function. Another study showed that patients receiving Ginkgo (40 mg three times a day) showed an improvement in their cognitive function compared to placebo, supporting the beneficial effect of this extract. However, misuse of this extract may lead to undesirable side effects such as a headache, bleeding, restlessness, diarrhea, vomiting and gastrointestinal disturbance.

Gene therapy
The methods for delivering genes to mammalian cells have stimulated great interest in the possibility of treating human disease by gene-based therapies. Up to date gene therapy is still not considered safe and effective but is under study. Gene therapy is commonly divided into two methods: ex vivo/ in vitro and in vivo. In *ex vivo,* method host cells are genetically modified to produce desired protein and then incorporated into the host. In vivo method involves the injection of vectors which carry the desired gene to replace the defective one.

The development of Nerve Growth Factor (NGF) gene therapy could slow the progression of AD either by reducing cholinergic cell loss or by augmenting neuronal function by directly stimulating cholinergic transmission in patients [59]. Cholinergic neurons of AD patients responded to NGF gene delivery, and also there was an increase in glucose uptake by cortical neurons. There were no extensive amyloid deposits in the cholinergic basal forebrain of patients with AD. Though cholinergic neurons show substantial neurofibrillary degeneration and NGF production is not reduced, its concentrations in the cholinergic basal forebrain are much lower than normal. This may be because of defects in NGF transportation in AD. These defects account for the lower concentrations of NGF in basal forebrain neurons which result in cholinergic neuronal degeneration. Delivery of NGF into cholinergic system by ex vivo gene therapy can be done to overcome this transport defect thereby sustaining cholinergic neurons; even NGF deficiency does not contribute to cholinergic cell loss, NGF gene delivery could be beneficial because it causes the augmentation of cholinergic transmission

Prevention
The AD has a long preclinical phase in which the process of dementia could begin before a diagnosis is clinically perceived. Therefore, it is necessary to identify patients at risk of early onset of the disease which would pose an advantage for clinical trials of agents thus reducing or delaying the late onset of the disease. The main importance of early diagnosis of AD is aimed at treating AD, and recognizing the disease early to initiate appropriate therapy and thus delaying functional and cognitive losses. Imaging assessment will be of great value in future enabling clinical trial results of new therapeutic agents and combination therapies delaying the onset of the disease [60].

It has been reported that even in relatively healthy older adults, high blood pressure and other stroke risk factors, such as diabetes, age and cardiovascular disease exist [61]. This can damage blood vessels in the brain and reduce the brain’s oxygen supply thereby disrupting nerve cells important for decision making, memory and verbal skills and tend to make the person more susceptible to the AD. Vitamin B12 (cobalamin) is involved in maintaining the function

of neurons and deficiency of this vitamin may result in neurological damage leading to memory loss, cognitive impairment and confusion.

Homocysteine (a toxic waste product produced during cellular metabolism) activates NMDA receptors and potentiates glutamate excitotoxicity and therefore initiates neuronal apoptosis [62]. Excess homocysteine is thought to be toxic to blood vessels and is considered to be associated with increased risk of AD. Folate and cobalamin levels can lower homocysteine. But the deficiency of cobalamin is believed to be a risk factor in the AD, and folate, vitamin B6, and B12 intake may increase cognitive decline [63]. Elderly patients (where VitB12 deficiency is most common) respond to cobalamin treatment as fully as younger patients, with complete or good partial resolution of neurological deficits. Chronic dementia responds poorly but should, nevertheless, be treated if there is a metabolic deficiency [64].
Scientists are researching to learn more about the possible relationships between AD and diabetes [65]. Abnormal glucose regulation, an essential element of diabetes, may also be involved in AD. In one analysis including more than 800 participants, researchers examined tests of five "cognitive systems" engaged with word and information processing speed, event memory, and the ability to recognize spatial patterns. The scientist found a 65 percent increase in the risk of developing AD among those with diabetes compared with non-diabetic. Too much insulin in the blood (which happens as a result of insulin resistance) may encourage inflammation and oxidative stress, both of which contribute to the damage seen in AD. It has been reported that keeping the brain active is associated with reduced AD risk [66].

During aging, oxidative damage can build up in nerve cells and result in a loss of cell function, which could contribute to AD. Some laboratory and population studies suggest that antioxidants from dietary supplements may provide some protection against this damage, but other studies show no effect [67]. Several trials are investigating whether two antioxidants — vitamins E and C — can slow cognitive decline and development of AD in healthy older individuals.

Even though no treatments, drugs, have been proven to prevent AD completely, people can take some precaution that might reduce the effect of possible AD risk factors [68]. These precautions include:

1: lowering cholesterol and homocysteine levels
2: lowering high blood pressure levels
3: controlling diabetes
4: exercising regularly
5: engaging in intellectually stimulating activities

All of these strategies are good to follow anyway as they lower the risk for other diseases and help maintain and improve overall health and living. It is widely perceived that prevention is better than cure and if there are some techniques which can help to avoid AD though they may not be thoroughly verified.

CONCLUSION

Alzheimer disease is characterized by a reduction of cortical neurons in the temporal and frontal cortex and the presence of neurofibrillary tangles and amyloid plaques [69-71]. ApoE4 allele, amyloid beta, and protein are predisposing markers found in AD [72]. Some factors influence the degeneration process involved in AD.

Although a 2017 study in the U.S. suggested that Ginkgo extract may be of some help in treating the symptoms of the AD [73] and vascular dementia, there is no evidence that Ginkgo biloba will prevent AD. Neuroimaging studies, although lacking the pathological specificity, Aids in identifying structural and functional changes in the brain such as cognitive decline.

Future therapies include agents acting on the amyloid protein, genetic predisposition, and treatment, hormone replacement therapy, cholinesterase inhibitors, the presence of ApoE2 and anti-radical therapies.

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