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Review Article

A REVIEW ON ALZHEIMER'S DISEASE: PATHOLOGY, MOLECULAR CONDITIONS, MANAGEMENT, AND CAUSES

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder that starts slowly, progressively leads to death and contributes to about 60-70% cases of dementia. AD is characterized with senile plaques (SPs) and neurofibrillary tangles (NFTs), and the major symptoms include problems with language, dis-orientation of words, unable to manage self-care, memory loss, and behavioral issues which gradually lead to completely lose bodily functions later. The actual cause for the disease is not known until date. Recent research shows distinct paths that closely try to reveal various cytoplasmic, genetic, behavioral, environmental, and epigenetic causes that may lead to the development of AD. Most likely all studies target the SPs, protein fragments called β-amyloid and NFTs, twisted fibers of a protein called tau. Since the exact causative mechanism is not yet clearly understood, ultimately finding a suitable treatment or management for the disease has also become an ominous challenge for researchers.

Keywords: Alzheimer's disease, Pathology, Phosphatase and tensin, Senile plaques, Neurofibrillary tangles.

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INTRODUCTION

Alzheimer's disease (AD) was first defined and described by Alois Alzheimer, a German psychiatrist and pathologist [1] at the 37th Conference of South-West German Psychiatrists in Tübingen, Alzheimer described his patient August D, a 51-year-old woman from Frankfurt showing symptoms of progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence. Plaques, neurofibrillary tangles (NFTs), and arteriosclerotic changes were found under the observation of necropsy. The word Alzheimer was originally used to refer pre-senile dementia; later it was used to describe the largest cause of primary dementia—senile dementia of the Alzheimer type [2]. AD is also known as just Alzheimer's, is a chronic neurodegenerative disease that gradually starts and gets worse over the course of time. It is the cause of 60-70% of cases of dementia* (*dementia is a general term for loss of memory and other cognitive abilities that are serious enough to interfere with the daily activities of life) [3]. Approximately, more than 24 million people worldwide are suspected to have dementia out of which most of them are thought to have AD. This includes about 11% of individual aged 65 and older and one-third of those who are 85 and older. It is also thought impact more than 15 million family members, friends, and caregivers. The most common early symptom is difficulty in remembering recent events. As the disease advances, the symptoms may include problems with language, dis-orientation of words, mood swings, loss of motivation, unable to manage self-care, and behavioral issues. Gradually, bodily functions are lost, ultimately leading to death. Although the speed of progression can vary, the average life expectancy following the diagnosis is nearly to last for 3-9 years only. During such conditions, people often withdraw from their family and society. The main causes of AD are still not well understood [4]. Most experts strongly believe that the destruction and death of nerve cells cause memory failure, personality changes, problems in carrying out daily activities, and other symptoms which further lead to the disease.

NEUROPATHOLOGY OF AD

The brain is composed of more than 100 billion nerve cells (neurons). Each nerve cell connects too many others to form communication networks. In addition to nerve cells, the brain includes cells specialized to support and nourish other cells. Some groups of nerve cells have special jobs such as thinking, learning and memory and some help us see, hear, smell and tell our muscles when to move. Brain cells operate like tiny factories. They receive supplies, generate energy, construct equipment and get rid of waste. Cells also process and store information and communicate with other cells. Keeping everything running requires coordination as well as large amounts of fuel and oxygen. Scientists believe that AD prevents certain parts of a cell's factory from functioning well, but they are not sure where the actual trouble starts. But just like a real factory, backups and breakdowns in one system cause problems in other areas. Similarly, in the brain the damage spreads and cells lose their ability to function and eventually die. Individuals with Alzheimer's have loads of plaques and tangles in the brain. Plaques are clumps of protein fragments called β-amyloid (Aβ) that occurs in the spaces between nerve cells. Tangles are twisted fibers of a protein called tau that buildup inside cells. Although autopsy studies show that most people develop some plaques and tangles as they age, those with AD tend to develop far more and in a predictable pattern, beginning in the areas important for memory before spreading to other regions. AD is characterized by the development of senile plaques (SPs) and NFTs, which are associated with neuronal destruction mostly occurring in the cholinergic neurons [5]. The actual role of plaques and tangles in AD is not yet known. Aβ plaques or SPs are clumps of insoluble peptides that result from the proteolytic cleavage of Aβ precursor protein (APP - the exact function of which is not known) and is found in extracellular deposits throughout the central nervous system (CNS). The APP is normally cleaved by three enzymes β-secretase, α-secretase, γ-secretase, respectively. Cleavage by the β-secretase followed by the γ-secretase yields a 40-amino acid peptide. In AD individuals, the variant of γ-secretase cleaves APP at the wrong position yielding a 39-42 amino acid peptide called Aβ42 or Aβ, which is insoluble and aggregates as identical clumps of peptides termed the Aβ plaques. Aβ is thought to interfere with neuronal function due to its stimulatory effect on free radical production resulting in oxidative stress and neuronal cell death. NFTs are paired helical filaments composed of tau protein which in normal cells are essential for axonal growth and development. These when hyperphosphorylated, the tau protein form tangles that are systematically deposited within neurons located in the hippocampus and medial temporal lobe, the parieto-temporal region, and the frontal association cortices leading to cell death [6].

The discovery of Aβ as the most important molecular constituent of the Senile plaques resulted in the formulation of the "amyloid cascade hypothesis" (ACH). ACH synthesizes histopathological and genetic information and posits that the deposition of the Aβ peptide in the brain parenchyma initiates a sequence of events that ultimately lead to AD dementia. Autosomal dominant mutations that cause early onset in familial AD occur in three genes: Presenilin 1 (PSEN1), PSEN2, and APP, respectively. This hypothesis has been modified over the years after various observations and studies and it has become clear that the correlation between dementia or other cognitive alterations and accumulation of Aβ in the brain in the form of amyloid plaques is not linear or stable, neither in humans [7] nor in mice [8]. Although Aβ-centric approaches contribute more to the research background, all that which reached Phase III clinical trials have failed for various drug based studies [9].

The limitations for the ACH include two major objectives; first, senile plaques and NFTs may be reactive products resulting from neurodegeneration in AD rather than being the cause for the disease [10], and second, there are not any general mechanism accepted to explain how the deposition of Aβ leads to the formation of NFTs.

CAUSES OF AD

AD involves the failure of nerve cells but it is still unknown why this dysfunction happens. However, certain risk factors which play a role in increasing the chances of developing AD have been identified.

AGE

The greatest known risk factor for Alzheimer's is increasing age. One in nine individuals of 65 and older age groups and nearly one-third of the total population with 85 and older age groups are increasingly subjected to AD.

FAMILY HISTORY

Research has illustrated that those individuals who have a twin, parent, brother, or sister with Alzheimer's are more likely to develop the disease than individuals who do not and not all members of the family acquire the disease.

FAMILIAL ALZHEIMER'S AND GENETICS

Two categories of genes influence a person to develop a disease normally: The risk genes and deterministic genes. Risk genes increase the likelihood to develop a disease but do not assure it will happen. Deterministic genes directly serve as the cause of the disease, assuring that anyone who inherits will develop that disease or disorder.

Researchers have found several genes that increase the risk of Alzheimer's. Some strong evidence shows that the Apolipoprotein E (ApoE) gene on chromosome 19 has gained much recent attention and it has been the first risk gene identified for AD. ApoE is a protein modulator of phospholipid transport that may have a role in synaptic remodeling. The common forms of the APOE gene are APOE-e2 and APOE-e3. A copy of APOE gene is inherited to the offspring from each parent and those who inherit a single copy of the APOE-e4gene have increased risk of developing AD and those who inherit both the copies of the gene are at an even higher risk, but not always. The postulated mechanisms of APOE-e4 include amyloid deposition and abnormal tau phosphorylation, a major component of NFTs.

Rare deterministic genes cause Alzheimer's in a few hundred extended families worldwide. These genes are estimated to account for <1% of cases. Individuals with these genes usually develop symptoms in their 40s or 50s.

OTHERS

Phosphatase and tensin (PTEN)

Homolog PTEN a dual-function phosphatase that possesses both lipid and protein phosphatase activities through its lipid phosphatase action (i.e., by hydrolyzing the crucial lipid secondary messenger PI (3,4,5) P3 to PI (3,4) P2 [11] inhibiting cell survival responses to PI3-kinase and Akt [12]. PTEN has been shown to modulate cell migration, growth, survival, and apoptosis and plays its major role as a tumor suppressor. More recent studies have shown that PTEN is expressed in neurons in human, mouse and rat brain [13-15] and suggest a functional role for PTEN in CNS development. PTEN is one of the major regulators of proliferation in neural stem cells and regulates neuronal migration, differentiation, soma size, and apoptosis. PTEN also negatively regulates insulin signaling. PTEN is also known to be a negative regulator of insulin resistance in peripheral tissues such as skeletal muscle and adipose tissue, where its down-regulation improves insulin sensitivity [16]. Akt is a vital promoter of neuronal survival in AD. PI3-kinase/Akt activation prevents Aβ-induced neurotoxicity in cells. Akt inhibits the enzyme glycogen synthase kinase 3 (GSK-3), which is thought to play a dual role in the regulation of both Aβ production and tau phosphorylation. PTEN by inhibiting Akt increases GSK-3 activity in cells and would promote tau and Ab pathologies via the signaling mechanism. Some researchers suggest that the gene encoding PTEN locates to the region of chromosome 10 linked to late-onset AD [17], further showing that it plays a functional role for PTEN in disease development. Several studies have reported that increases in Akt activity in AD brain [18,19], and more recent observations show that this may be due to reductions in PTEN levels [20].

MITOCHONDRIAL DYSFUNCTION

Aβ is considered as a potential mitochondrial poison that affects the synaptic pool. In individuals carrying AD, exposure to Aβ will inhibit certain mitochondrial enzymes like cytochrome C in the brain. The accumulation of Aβ in damaged mitochondria of AD individuals can be found intra-neuronally in the brain [21].

CELL-CYCLE RE-ENTRY

Many scientists hypothesized that the failure in the normal suppression of cell cycle as one of the reasons for the onset of AD [22]. Bio-markers of cell-cycle re-entry especially in G1-S-phase boundary can be detected in all stages of AD and even in mild cognitive impairment [23,24].

CALPAIN-CATHEPSIN HYPOTHESIS

Autophagic vacuoles or granulovacuolar degenerations can be seen in degenerating neurons of AD patients. This probably is a causative connection between neuronal death and autophagy failure. Many scientists proposed that an age-dependent oxidative stress affects autophagic-lysosomal system through cleavage and carbonylated heat-shock protein 70.1 (Hsp70.1). Membrane lipids are vulnerable to the oxidative stresses, and they generate toxic peroxidation products that can carbonylated Hsp70.1. Many evidence suggests that Hsp70.1 is a molecular chaperone which repairs damaged proteins and maintains lysosomal integrity. Impairments of lysosomal functions and stabilization are found to be driven by calpain-mediated cleavage of carbonylated Hsp70.1, which results in lysosomal permeabilization or rupture releasing the cell degradation enzymes, cathepsins which eventually lead to the AD. This hypothesis is called as calpain-cathepsin hypothesis, which is recently put forward by the scientists and currently most acceptable [25].

DIAGNOSIS OF AD

Diagnosing Alzheimer's requires careful medical evaluation, including a thorough medical history, mental status testing, a physical and neurological exam. Magnetic resonance imaging (MRI), computed tomography (CT), single photon emission CT, and positron emission tomography which can be used in the determining cerebral pathology in AD patients. Chronic cerebrospinal venous insufficiency has been evaluated using echo color Doppler (ECD), ultrasound Doppler, ultrasound Doppler sonography, transcranial color-coded sonography, and even MRI. Application of ECD technique to detect neurodegeneration can be used to find AD in patients. During a neurological examination,

Table 1: Medications for AD [26]

Medication*	Usage	Adverse effects (%)	General dosage
Acetyl cholinesterase inhibitors		Nausea, vomiting, and diarrhoea; cardiovascular and neurologic adverse effects	
Donepezil (aricept)	Approved for use in all stages of AD	Adverse effect (15.1-71.3)	10 mg/day
Galantamine (razadyne)	Moderate to severe stage of AD	Adverse effect (31.9-55)	8 mg twice per day, or 16 mg extended release formulation once per day
Rivastigmine (exelon)	Moderate to severe stage of AD	Adverse effect (20.1-78)	6 mg orally twice per day or 9.5 mg/24 hrs patch
Tacrine (cognex)	Tacrine is no longer available because of safety and tolerability concerns		
NMDA receptor antagonist		Dizziness, confusion, headache, diarrhoea, vomiting	
Memantine (namenda)	Moderate to severe stage of AD	Adverse effects and dropout rates not statistically different from placebo	10 mg twice per day
Monoamine oxidase type B inhibitor			
Selegiline	There is not enough evidence to recommend selegiline for the treatment of AD		

NMDA: N-methyl-D-aspartate, *medications do not reverse the symptoms of dementia but may slow their course, AD: Alzheimer's disease

the problems that signal brain cells to cause disorders other than Alzheimer's will be evaluated. The doctor will look for signs of small or large strokes, Parkinson's disease, brain tumors, fluid accumulation on the brain, and other illnesses that may impair memory or thinking.

AD MANAGEMENT

Numerous studies have assessed factors that may affect the incidence of AD, and many prominent studies have shown the closest association of the disease, but they have not proven the relationship and it is still not clear whether it would reduce the risk of severity of the AD. Certain epidemiological factors of AD are associated with dietary habits, cardiovascular diseases, and intellectual activities. Presently, AD medications target only secondary risk factors such as hypercholesterolemia, hypertension, and smoking and very few drugs have shown little success to arrest the progression of AD.

Hormone replacement therapy has also been proposed for treating AD, but many researchers suggested that it still increases dementia. Change in lifestyle of AD patients is recommended for a possible management strategy of AD. Some research papers also suggest that caffeine, tea, red wine, cocoa, Vitamin A, C, E, folic acid and minerals such as selenium and Zinc are effective against AD management.

Acetylcholinesterase inhibitors are first-line agents for the treatment of mild to moderate AD, per existing guidelines. Acetylcholinesterase inhibitors reversibly bind and degrade acetylcholine which is involved in memory by inactivating the enzyme [27]. A N-methyl-D-aspartate (NMDA) receptor antagonist memantine prevents excessive glutamatergic activity. The Cochrane review showed the memantine activity at 20 mg/day dosage for 6 months would slightly improve the ability to do activities of daily living and cognition in patients with moderate to severe AD. Selegiline (Eldepryl) is a monoamine oxidase type B inhibitor with minimal anticholinergic effects. Currently, there is not much evidence to recommend selegiline for the treatment of AD. Antipsychotics are not approved by the Food and Drug Administration for the treatment of AD, though they are commonly used to treat behavioral symptoms. Evidence suggests that olanzapine (Zyprexa) and risperidone (Risperdal) reduce aggression, and risperidone reduces psychosis in patients with AD [28]. The other potential treatments for AD include resveratrol, a compound from the skin of red grapes that may have beneficial effects on aging, a NMDA receptor antagonist that may also weakly inhibit acetylcholinesterase, which in turn may improve cognitive performance of the affected individual and is currently in testing process of phase 3 trials.

A recent consensus statement from the National Institutes of Health's State-of-the-Science Conference on Preventing AD and cognitive decline concluded that the current evidence is insufficient to support the association of any modifiable factor, pharmacologic agent, or dietary supplement with a reduction in the risk of AD [29]. The recent updates on the advances in treating AD include the Anti-amyloid therapy involves the usage of drugs with variant actions on different mechanisms for example: Enhance the clearance of Aβ, reduce the production of Aβ and inhibit the accumulation of Aβ; γ-secretase inhibitors (GSI) and modulators; using kinase inhibitors to decrease the activity of kinase enzyme the interaction between GSK3ββ and protein phosphate 2 (PP2A) increases the tau hyper-phosphorylation and NFT generation; therapy for mitochondrial dysfunction; anticholinergic therapy by the administration of choline inhibitors [30].

CONCLUSION

AD pathogenesis appears to be initiated by the production, accumulation and oligomerization of Aβ protein (Aβ), forming extracellular amyloid plaques that lead to neuropathological signs of the disease including tangles of intracellular hyperphosphorylated tau, gliosis, synaptic dysfunction and eventually cell death. This neurodegeneration association with AD starts many years before the clinical onset, during this preclinical phase the plaque and tangle increase in the brain until a threshold level is reached and beyond which the cognitive impairment become manifested. Different regions of the brain show differential vulnerability to AD, with some regions being particularly affected and others relatively resistant, both plaques and tangles occur first in the areas of the brain involved in learning, memory, and emotional behaviors. Other areas such as the cerebellum have relatively high resistant to the neuronal damage with little or no tangle and plaque formation, tau pathology or neuronal loss. Epigenetic mechanisms show a wide range of important cognitive and neurobiological processes in the brain such as neurogenesis and brain development, neuronal activity, learning and memory, and circadian rhythm and disruption to these processes is likely to play a profound role in health and disease. Several epidemiological and clinical features of AD suggest an epigenetic contribution and these include monozygotic twin discordance in both AD diagnosis by Plomin *et al*., 1994 [31]; evidence of parent-of-origin effects in both disease transmission by Edland *et al*., 1996 [32] and genetic association studies by Bassett *et al*., 2006 [33]. Recent literature shows that there are striking age-associated epigenetic changes in the human brain including within the APP and microtubule-associated protein tau genes.

The causes that contribute to AD are potentially observed by various studies; on the other hand, many potential therapeutic agents are currently under investigation for the treatment and management of AD. APP and the enzymes involved in Aβ formation are thought to contribute much to the genetic forms of the disease. The methods to

reduce amyloid plaque severity, by altering the amyloid metabolism are being evaluated in the recent studies. Immunotherapy to promote the clearance of Aβ from the CNS is being assessed gradually. The PTEN can be assessed as the new potential target for the prevention of AD. In addition to the varied role of insulin in peripheral tissues, it has profound effects in the CNS, where it regulates various key physiological functions such as energy homeostasis, food intake, reproductive endocrinology, peripheral insulin actions, sympathetic activity and even memory, and learning [34]. Dysfunction of the insulin-signaling pathway in the CNS has been contributing to several pathophysiological conditions, including hyperphagia, obesity, and type 2 diabetes. To add on to these complications, there is a wide recognition that impaired insulin signaling and glucose metabolism in the brain acts as a mediator of chronic neurodegenerative disease AD. The molecular mechanism of insulin resistance in neurons is largely unknown. In peripheral tissues, such as skeletal muscle, liver, and adipose the drug development to treat neuronal insulin resistance is non-productive. PTEN and Src homology 2 domain contain inositol 5′ phosphatase 2 (SHIP2) and have been widely suggested as the negative regulators of insulin/PI3K signaling [35]. There is a large recognition that impaired insulin actions in the brain act as mediators of AD and thus AD is also characterized as a brain-specific form of diabetes. AD is termed as "type 3 diabetes" and has been proposed by Steen *et al.* in 2005 [36]. Although there is growing wealth and knowledge on the data on the backgrounds of AD, it has not been enough to present a single or cohesive picture about its causes nor the treatments till date. In the most recent technology, molecular docking studies are performed to detect the molecular interactions, active site prediction, and drug interaction based studies; these advanced techniques make help in the better understanding of molecular basis of AD [37].

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