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A Review on Causes and Treatment of Alzheimer's Disease

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ABSTRACT
Alzheimer's disease is one of the most devastating brain disorders of elderly humans. It is an undertreated and under-recognized disease that is becoming a major public health problem. The last decade has witnessed a steadily increasing effort directed at discovering the etiology of the disease and developing pharmacological treatment. Recent developments include improved clinical diagnostic guidelines and improved treatment of both cognitive disturbance and behavioral problems. Symptomatic treatment mainly focusing on cholinergic therapy has been clinically evaluated by randomized, double-blind, placebo- controlled, parallel-group studies measuring performance-based tests of cognitive function, activities of daily living, and behavior. Cholinesterase inhibitors, including donepezil, tacrine, rivastigmine, and galantamine are the recommended treatment of cognitive disturbance in patients with Alzheimer's disease. The role of estrogen replacement, anti-inflammatory agents, and antioxidants is controversial and needs further study. Antidepressants, antipsychotics, mood stabilizers, anxiolytics, and hypnotics are used for the treatment of behavioral disturbance. Future directions in the research and treatment of patients with Alzheimer's disease include: applying functional brain imaging techniques in early diagnosis and evaluation of treatment efficacy: development of new classes of medications working on different neurotransmitter systems (cholinergic, glutamatergic, etc), both for the treatment of the cognitive deficit and the treatment of the behavioral disturbances, and developing preventive methods (amyloid p-peptide immunizations and inhibitors ofB-secretase and y-secretase).

KEY WORDS: Alzheimers Disease, Apolipoprotein E4, Cholinestrase inhibitor, Antioxidant.

I. INTRODUCTION:

Dementia is a general term that refers to a decline in cognitive ability severe enough to interfere with activities of daily living. Alzheimer's disease (AD) is the most common type of dementia, accounting for at least two-thirds of cases of dementia in people age 65 and older. Alzheimer's disease is a neurodegenerative disease with insidious onset and progressive impairment of behavioral and cognitive functions including memory, comprehension, language, attention, reasoning, and judgment. It is the sixth leading cause of death in the United States. Onset before 65 years of age (early onset) is unusual and seen in less than 10% of Alzheimer's disease patients. There is no cure for Alzheimer's disease, although there are treatments available that may improve some symptoms.

Symptoms of Alzheimer's disease depend on the stage of the disease. Alzheimer's disease is classified into preclinical or presymptomatic, mild, and dementia-stage depending on the degree of cognitive impairment. These stages are different from the DSM-5 classification of Alzheimer's disease. The initial and most common presenting symptom is episodic short-term memory loss with relative sparing of long-term memory and can be elicited in most patients even when not the presenting symptom. Short-term memory impairment is followed by impairment in problem-solving, judgment, executive functioning, lack of motivation and disorganization, leading to problems with multitasking and abstract thinking. In the early stages, impairment in executive functioning ranges from subtle to significant. This is followed by language disorder and impairment of visuospatial skills. Neuropsychiatric symptoms like apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are also common in the mid to late stages. Difficulty performing learned motor tasks (dyspraxia), olfactory dysfunction, sleep disturbances, extrapyramidal motor signs like dystonia, akathisia, and parkinsonian symptoms

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occur late in the disease. This is followed by primitive reflexes, incontinence, and total dependence on caregivers.

ETIOLOGY:

The main neuropathological features of AD appear to be senile plaques and neurofibrillary tangles. The senile plaques seem to develop first in brain areas associated with cognition, and spread to other cortical areas as the disease progresses. The senile plaques consist, among other components, of insoluble deposits of amyloid p-peptide (Aß), a fragment of the amyloid precursor protein (APP). Aß peptide is generated from APP by two consecutive cleavage events: proteolytic activity by [l-secretase generates one end of the Ap peptide, while y secretase generates the other end, also by proteolysis. There appear to be two types of Aß: a longer species, Af42, and a shorter species, Aß40. Aß42 seems to be deposited initially and may have a role in initiating the events that ultimately lead to amyloid deposition. It is still not clear if the senile plaques are the cause or a by-product of AD, although there are increasing data that dysfunction in the metabolism of APP with subsequent increase in the insoluble Aß is responsible for AD. AB seems toxic to the neuron either directly, or indirectly by causing inflammation or increasing the production of free radicals.

EPIDEMIOLOGY:

Alzheimer's disease has a significant impact on individuals worldwide. According to epidemiological studies, it is estimated that around 50 million people globally are living with dementia, and the majority of these cases are attributed to Alzheimer's disease. The prevalence of Alzheimer's increases with age, with the risk doubling approximately every five years after the age of 65. However, it's important to note that Alzheimer's can also affect younger individuals, although this is relatively rare. In terms of gender, women tend to be more commonly affected by Alzheimer's compared to men.

PATHOPHYSIOLOGY:

Alzheimer's disease is characterized by an accumulation of abnormal neuritic plaques and neurofibrillary tangles.

Plaques are spherical microscopic lesions that have a core of extracellular amyloid beta-peptide surrounded by enlarged axonal endings. Beta-amyloid peptide is derived from a transmembrane protein known as an amyloid precursor protein (APP). The beta-amyloid peptide is cleaved from APP by the action of proteases named alpha, beta, and gamma-secretase. Usually, APP is cleaved by either alpha or beta-secretase and the tiny fragments formed by them are not toxic to neurons. However, sequential cleavage by beta and then gamma-secretase results in 42 amino acid peptides (beta-amyloid 42). Elevation in levels of beta-amyloid 42 leads to aggregation of amyloid that causes neuronal toxicity. Beta-amyloid 42 favors the formation of aggregated fibrillary amyloid protein over normal APP degradation. APP gene is located on chromosome 21, one of the regions linked to familial Alzheimer's disease. Amyloid deposition occurs around meningeal and cerebral vessels and gray matter in Alzheimer's disease. Gray matter deposits are multifocal and coalesce to form milliary structures called plaques. However, brain scans have noted amyloid plaques in some persons without dementia and then other persons had dementia but brain scans did not find any plaques.

Neurofibrillary tangles are fibrillary intracytoplasmic structures in neurons formed by a protein called tau. The primary function of the tau protein is to stabilize axonal microtubules. Microtubules run along neuronal axons and are essential for intracellular transport. Microtubule assembly is held together by tau protein. In Alzheimer's disease, due to aggregation of extracellular beta-amyloid, there is hyperphosphorylation of tau which then causes the formation of tau aggregates. Tau aggregates form twisted paired helical filaments known as neurofibrillary tangles. They occur first in the hippocampus and then may be seen throughout the cerebral cortex. Tau-aggregates are deposited within the neurons. There is a staging system developed by Braak and Braak based on the topographical staging of neurofibrillary tangles into 6 stages, and this Braak staging is an integral part of the National Institute on Aging and Reagan Institute neuropathological criteria for the diagnosis of Alzheimer disease. Tangles are more strongly correlated to Alzheimer's than the plaques.

SIGNS AND SYMPTOMS:

Alzheimer’s disease is a progressive condition, meaning that the symptoms get worse over time. Memory loss is a key feature, and this tends to be one of the first symptoms to develop.
The symptoms appear gradually, over months or years. If they develop over hours or days, a person may require medical attention, as this could indicate a Stroke.

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Symptoms of Alzheimer's disease include:

- Memory loss: A person may have difficulty taking in new information and remembering information. This can lead to:
- repeating questions or conversations.
- losing objects.
- forgetting about events or appointments.
- wandering or getting lost.
- Cognitive deficits: A person may experience difficulty with reasoning, complex tasks, and judgment. This can lead to:
- a reduced understanding of safety and risks.
- difficulty with money or paying bills.
- difficulty making decisions.

Problems with recognition: A person may become less able to recognize faces or objects or less able to use basic tools. These issues are not due to problems with eyesight.

Problems with spatial awareness: A person may have difficulty with their balance, trip over, or spill things more often, or they may have difficulty orienting clothing to their body when getting dressed.

Problems with speaking, reading, or writing: A person may develop difficulties with thinking of common words, or they may make more speech, spelling, or writing errors.

Personality or behavior changes: A person may experience changes in personality and behavior that include:

- becoming upset, angry, or worried more often than before.
- a loss of interest in or motivation for activities they usually enjoy.
- a loss of empathy.
- compulsive, obsessive, or socially inappropriate behavior.

RISK FACTORS:

Researchers believe there is not a single cause of Alzheimer's disease. It likely develops from multiple factors, such as genetics, lifestyle and environment. Scientists have identified factors that increase the risk of Alzheimer's. While some risk factors like age, family history and genetics can't be changed, emerging evidence suggests there may be other factors people can influence.

Age

The greatest risk for Alzheimer's disease is age. After age 65, a person's risk of developing the disease increases dramatically. About a third of people age 85 or older have Alzheimer's.

Family history

Researchers have learned that people who have a parent, brother or sister with Alzheimer's are more likely to develop it than those who do not. The risk increases if more than one family member has the disease.

Genetics

Two types of genes influence whether a person develops a disease: risk genes and deterministic genes. Risk genes increase the chance of developing a disease but do not guarantee it will happen. Deterministic genes cause a disease. This means anyone who inherits a deterministic gene will develop a disorder.

Rare deterministic genes cause Alzheimer's in a few hundred extended families worldwide. Scientists estimate these genes cause less than 1% of cases. Individuals with these genes usually develop symptoms in their 40s or 50%.

Hispanic people,Black American and Women

Black Americans are about twice as likely as White Americans to have Alzheimer's or another dementia, and Hispanic Americans are one-and-a-half times as likely. Though no one knows the exact reason for these differences, researchers believe they are related to disparities produced by the historic and continued marginalization of Black and Hispanic people in the United States disparities between older Black and Hispanic populations and older White populations in life experiences, socioeconomic indicators and, ultimately, health conditions.

Additionally, women are more likely to develop Alzheimer's than men. This difference may be explained, in part, by the fact that women live longer. However, researchers are exploring how genetic differences may impact Alzheimer's risk differently in men and women.

DIAGNOSIS:

To receive a diagnosis of Alzheimer's, a person will be experiencing memory loss, cognitive decline, or behavioral changes that are affecting their ability to function in their daily life.

Friends and family may notice the symptoms of dementia before the person themselves.

There is no single test for Alzheimer's disease. If a doctor suspects the presence of the condition, they will ask the person — and sometimes their family or caregivers about their symptoms, experiences, and medical history.

The doctor may also carry out the following tests:

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- cognitive and memory tests, to assess the person's ability to think and remember.
- neurological function tests, to test their balance, senses, and reflexes.
- blood or urine tests.
- a CT Scan or MRI Scan of the brain.
- genetic testing.

TREATMENT AND MANAGEMENT:

Thre is no cure for Alzheimer's disease. Only symptomatic treatment is available.

Two categories of drugs are approved for the treatment of Alzheimer's disease: cholinesterase inhibitors and partial N-methyl D-aspartate (NMDA) antagonists.

Cholinesterase Inhibitors

Cholinesterase inhibitors act by increasing the level of acetylcholine; a chemical used by nerve cells to communicate with each other and is important for learning, memory and cognitive functions. Of this category, 3 drugs: donepezil, rivastigmine, and galantamine are FDA-approved for the treatment of Alzheimer's disease.

Donepezil can be used in all stages of Alzheimer's disease. Galantamine and rivastigmine are approved for treatment in MCI and Dementia stage. Donepezil and galantamine are rapid, reversible inhibitors of acetylcholinesterase. Rivastigmine is a slow, reversible inhibitor of acetylcholinesterase and butyrylcholinesterase. Donepezil is usually preferred of all because of once-daily dosing. Galantamine is available as a twice-daily tablet or as a once-daily extended-release capsule. It cannot be used in end-stage renal disease or severe liver dysfunction. Rivastigmine is available in an oral and transdermal formulation. The most common side effects of cholinesterase inhibitors are gastrointestinal-like nausea, vomiting, and diarrhea. Sleep disturbances are more common with donepezil. Due to increased vagal tone, bradycardia, cardiac conduction defects, and syncope can occur, and these medications are contraindicated in patients with severe cardiac conduction abnormalities.

Partial N-Methyl D-Aspartate(NMDA) Memantine

Partial N-Methyl D-aspartate (NMDA) antagonist memantine blocks NMDA receptors and slows intracellular calcium accumulation. It is approved by the FDA for treating moderate to severe Alzheimer's disease. Dizziness, body aches, headache, and constipation are common side effects. It can be taken in combination with cholinesterase inhibitors.

It is also important to treat anxiety, depression, and psychosis, which is often found in the mid to late stages of Alzheimer's disease. Avoid tricyclic antidepressants, because of their anticholinergic activity. Antipsychotics are used for acute agitation, only if the patient or caregiver have been exhausted. However, their limited benefits should be weighed against the small risk of stroke and death.

Environmental and behavioral approaches are beneficial especially in managing behavioral problems. Simple approaches such as maintaining a familiar environment, monitoring personal comfort, providing security objects, redirecting attention, removing doorknobs and avoiding confrontation can be very helpful in managing behavioral issues.

To minimize caregiver burden, mild sleep disturbances can be reduced by providing exposure to sunlight and providing daytime exercise.

The expected benefits of the treatment are modest. Treatment should be stopped or modified if no significant benefits or if intolerable side effects.

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