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Review Article

Alzheimer's Diseases

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ABSTRACT

Alzheimer's disease (AD) is a disorder that causes degeneration of the cells in the brain and it is the main cause of dementia, which is characterized by a decline in thinking and independence in personal daily activities. AD is considered a multifactorial disease: two main hypotheses were proposed as a cause for AD, cholinergic and amyloid hypotheses. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease. Currently, there are only two classes of approved drugs to treat AD, including inhibitors to cholinesterase enzyme and antagonists to N-methyl d-aspartate (NMDA), which are effective only in treating the symptoms of AD, but do not cure or prevent the disease. Nowadays, the research is focusing on understanding AD pathology by targeting several mechanisms, such β-amyloid as abnormal tau protein metabolism, , inflammatory response, and cholinergic and free radical damage, aiming to develop successful treatments that are capable of stopping or modifying the course of AD. This review discusses currently available drugs and future theories for the development of new therapies for AD, such as disease- modifying therapeutics (DMT), chaperones, and natural compounds.

INTRODUCTION

Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia. It is a progressive disease beginning with mild memory loss and possibly leading to loss of the ability to carry on a conversation and respond to the environment. Alzheimer's disease involves parts of the brain that control thought, memory, and language.

More than 6 million Americans, many of them age 65 and older, are estimated to have Alzheimer's disease. That's more individuals living with Alzheimer's disease than the population of a large American city. Many more people experience Alzheimer's in their lives as family members and friends of those with the disease. The symptoms of Alzheimer's disease — changes in thinking, remembering, reasoning, and behavior — are known as dementia. That's why

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Alzheimer's is sometimes referred to as "dementia." Other diseases and conditions can also cause dementia, with Alzheimer's being the most common cause of dementia in older adults.
Alzheimer's disease is not a normal part of aging. It's the result of complex changes in the brain that start years before symptoms appear and lead to the loss of brain cells and their connections.

ALZHEIMER'S DISEASES NEUROPHOLOGY:

There are two types of neuropathological changes in AD which provide evidence about disease progress and symptoms and include: (1) positive lesions (due to accumulation), which are characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of AD patients. In addition to (2) negative lesions (due to losses), that are characterized by large atrophy due to a neural, neuropil, and synaptic loss. Besides, other factors can cause neurodegeneration such as neuroinflammation, oxidative stress, and injury of cholinergic neurons.

1.Senile Plaques (SP):

The senile plaques are extracellular deposits of beta-amyloid protein (Aβ) with different morphological forms, including neuritic, diffuse, dense-cored, or classic and compact type plaques. Proteolytic cleavage enzymes such as β-secretase and γ-secretase are responsible for the biosynthesis of Aβ deposits from the transmembrane amyloid precursor protein (APP) These enzymes cleave APP into several amino acid fragments: 43, 45, 46, 48, 49, and 51 amino acids, which reach the final forms Aβ40 and Aβ42. There are several types of Aβ monomers, including large and insoluble amyloid fibrils which can accumulate to form amyloid plaques and soluble oligomers that can spread throughout the brain. Aβ plays a major role in neurotoxicity and neural function, therefore, accumulation of denser plaques in the hippocampus, amygdala, and cerebral cortex can cause stimulation of astrocytes and microglia, damage to axons, dendrites, and loss of synapses, in addition to cognitive impairments.

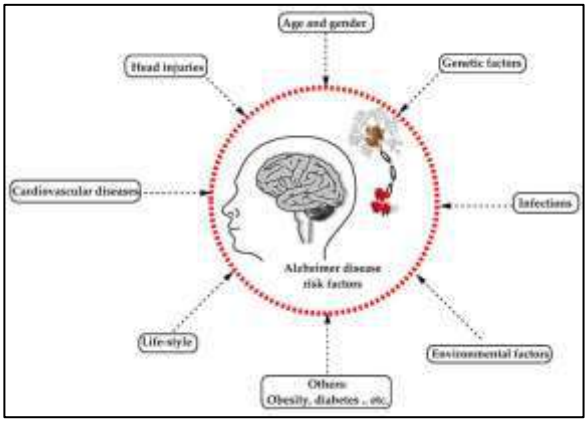
2.Neurofibrillary Tangles (NFTs):

NFT are abnormal filaments of the hyperphosphorylated tau protein that in some stages can be twisted around each other to form paired helical filament (PHF) and accumulate in neural perikaryal cytoplasm, axons, and dendrites, which cause a loss of cytoskeletal microtubules and tubulin-associated proteins. The hyperphosphorylated tau protein is the major constituent of NFTs in the brains of AD patients, and its evolution can reflect NFTs morphological stages, which include: (1) pre-tangle phase, one type of NFT, where phosphorylated tau proteins are accumulated in the somatodendritic compartment without the formation of PHF, (2) mature NFTs, which are characterized by filament aggregation of tau protein with the displacement of the nucleus to the periphery part of the soma, and (3) the extracellular tangles, or the ghost NFTs stage, that results from a neuronal loss due to large amounts of filamentous tau protein with partial resistance to proteolysis .

3.Synaptic Loss:

A synaptic damage in the neocortex and limbic system causes memory impairment and generally is observed at the early stages of AD. Synaptic loss mechanisms involve defects in axonal transport, mitochondrial damage, oxidative stress, and other processes that can contribute to small fractions, like the accumulation of Aβ and tau at the synaptic sites. These processes eventually lead to a loss of dendritic spines, pre-synaptic terminals, and axonal dystrophy [26]. Synaptic proteins serve as biomarkers for the detection of synapses loss, and severity, such as neurogranin, a postsynaptic neuronal protein, vicenin-like protein-1 (VILIP-1), and synaptosome.

CAUSES AND RISK FACTORS OF ALZHEIMER'S DISEASE



AD has been considered a multifactorial disease associated with several risk factors (Figure) such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors (heavy metals, trace metals, and others). The underlying cause of pathological changes in Alzheimer's disease (Aβ, NFTs, and synaptic loss) is still unknown. Several hypotheses were proposed as a cause for AD but two of them are believed to be the main cause: some believe that an impairment in the cholinergic function is a critical risk factor for AD, while others suggest that alteration in amyloid β-protein production and processing is the main initiating factor. However, at present, there is no accepted theory for explaining the AD pathogenesis.

Alzheimer's Disease Risk Factors :

Aging The most important risk factor in AD is aging. Younger individuals rarely have this disease, and most AD cases have a late onset that starts after 65 years of age . Aging is a complex and irreversible process that occurs through multiple organs and cell systems with a reduction in the brain volume and weight, a loss of synapses, and ventricles' enlargement in specific areas accompanied by SP deposition and NFT. Moreover, several conditions might emerge during aging such as glucose hypometabolism, cholesterol dishonesties, mitochondria dysfunction, depression, and cognitive decline. These changes also appear in normal aging, which makes it difficult to distinguish the cases in early AD . AD can be divided based on age of onset into early-onset AD (EOAD), the rare form with around 1–6% of cases, in which most of them are familial AD characterized by having more than one member in more than one generation with AD, and ranges from 30–60 or 65 years. The second type is the late-onset AD (LOAD), which is more common with age of onset above 65 years. Both types may occur in people who have a family with a positive history of AD and families with a late-onset disease .

Genetics Genetic factors were discovered over the years and were found to play a major role in the development of AD. 70% of the AD cases were related to genetic factors: most cases of EOAD are inherited in an autosomal dominant pattern and mutations in the dominant genes such as Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), Presenilin-2 (PSEN-2), and apolipoprotein E (ApoE) are associated with AD . Amyloid Precursor Protein (APP) APP is a type I transmembrane protein cleaved by α-, β-, and γ-secretase to release Aβ and other proteins and is encoded by the APP gene on chromosome 21. Thirty mutations have been found in the APP gene in which twenty-five of them are related to AD and cause an ccumulation of Aβ with elevated amounts. Meanwhile, there is one protective mutation, A673T, which protects against AD by decreasing Aβ, Aβ40, and Aβ42 secretion. All mutations surround the secretase cleavage site, for example, the KM670/671NL mutation in mouse models has shown an increasing level of amyloid plaques in the hippocampus and cortex with no NFTs. Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2) PSEN1 and PSEN2 genes are also the autosomal dominant form of EOAD located on chromosomes 14 and 1, respectively. PSEN-2 and PSEN-1 are homologous, with 67% similarity,

with a difference in the N-terminus and the hydrophilic region. Mutation in PSEN1 gene is more common, with more than 200 mutations, while a rare form with less than 40 mutations was identified in the PSEN2 gene .

Environmental Factors Aging and genetic risk factors cannot explain all cases of AD. Environmental risk factors including air pollution, diet, metals, infections, and many others may induce oxidative stress and inflammation and increase the risk for developing AD. Herein, we report the most important environmental factors and their relationships with AD .

Air Pollution

The air pollution is characterized by modifying the nature of the atmosphere through the introduction of chemical, physical, or biological pollutants.

Diet

In recent years, the number of studies on the role of nutrition in AD have been increased. Several dietary supplements such as antioxidants, vitamins, polyphenols, and fish were reported to decrease the risk of AD, whereas saturated fatty acids and high-calorie intake were associated with increasing the risk of AD.

Metals

Metals are found in nature and biological systems and can be divided into bio-metals that have a physiological function in living organisms (e.g., copper, zinc, and iron), and toxicological metals which do not possess any biological function (e.g., aluminum and lead) [82]. Aluminum is used significantly in the industries such as processed foods, cosmetics, medical preparations, medicines, and others. In the body, aluminum is bound to plasma transferrin and to citrate molecules that can mediate the transfer of aluminum to the brain.

Medical Factors Several risk factors are related to the development of Alzheimer's disease. Adding to this list, older people with AD usually have medical conditions such as cardiovascular disease (CVD), obesity, diabetes, and others. All of these conditions are associated with increased risk of AD.

Cardiovascular Disease (CVDs)

CVDs are recognized as an important risk factor for AD, such as the stroke that is associated with increased risk of dementia due to a neural tissue loss, which enhances degenerative effect and influences amyloid and tau pathology. Atrial fibrillation also causes embolisms which leads to stroke and a decrease in memory and cognitive functions. Moreover, heart failure affects the pumping function of the heart and results in insufficient blood supply to the body and hypo-perfusion of the brain that leads to hypoxia and neural damage.

Obesity and Diabetes

Obesity is a term used for too much body fat in individuals due to consuming more calories than they burn and can be calculated by using the body mass index (BMI). Increasing the body fat is associated with a decreased brain blood supply which promotes brain ischemia, memory loss, and vascular dementia. The obesity, unhealthy diet, and other factors can cause impaired glucose tolerance (IGT) or diabetes, which is characterized by hyperglycemia that affects peripheral tissues and blood vessels. Chronic hyperglycemia can induce cognitive impairment as a result of increasing amyloid-beta accumulation, oxidative stress, mitochondrial dysfunction, and neuroinflammation.

ETIOLOGY

Alzheimer's disease is a gradual and progressive neurodegenerative disease caused by neuronal cell death. It typically starts in the entorhinal cortex in the hippocampus. There is a genetic role identified for both early and late-onset Alzheimer's disease. Trisomy 21 is a risk factor for early-onset dementia. Several risk factors

have been associated with Alzheimer's disease. Increasing age is the most important risk factor for Alzheimer's disease. Traumatic head injury, depression, cardiovascular and cerebrovascular disease, higher parental age, smoking, family history of dementia, increased homocysteine levels and presence of APOE e4 allele are known to increase the risk of Alzheimer's disease. Higher education, use of estrogen by women, use of anti-inflammatory agents, leisure activities like reading or playing musical instruments, healthy diet and regular aerobic exercise is known to decrease the risk of Alzheimer's disease. Having a first-degree relative with Alzheimer's disease increases the risk of developing Alzheimer's disease by 10% to 30%. Individuals with 2 or more siblings with late-onset Alzheimer disease increase their risk of getting Alzheimer's disease by 3-fold as compared to the general population.

EPIDEMIOLOGY

Alzheimer's disease is typically a disease of old age. The global prevalence of dementia is reported to be as high as 24 million and is predicted to increase 4 times by the year 2050. The estimated health care cost of Alzheimer's disease is $172 billion per year in the United States alone. In 2011, the United States had an estimated 4.5 million people age sixty-five and above, living with clinical Alzheimer's disease. The incidence of Alzheimer's disease doubles every 5 years, after the age of 65. Age-specific incidence increases significantly from less than 1% per year before 65 years of age to 6% per year after 85 years of age. Prevalence rates increase from 10% after the age of 65 to 40 % after the age of 85. Incidence rates of Alzheimer's disease are slightly higher for women, especially after 85 years of age.

PATHOPHYSIOLOGY

Alzheimer's disease is characterized by an accumulation of abnormal neurotic 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 miliary 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. Another feature of Alzheimer's disease is granulovacuolar degeneration of hippocampal pyramidal cells by amyloid angiopathy. Some reports indicate that cognitive decline correlates more with a decrease in the density of presynaptic boutons from pyramidal neurons in laminae III and IV, rather than an increase in the number of plaques. Neuronal loss in Nucleus Basalis of Meyner, leading to low Acetylcholine has also been noted. Vascular contribution to the neurodegenerative process.

HISTORY AND PHYSICAL:

A good history and physical examination are the keys to diagnosis. It is also important to take a history from family and caregivers, as some

patients may not have information about their illness. It is important to characterize emerging and early symptoms to distinguish them from other types of dementia. It is important to obtain a good assessment of functional abilities, such as basic and individual activities of daily living.

A complete physical examination with a detailed neurological examination and a mental status examination is necessary to assess the stage of the disease and exclude other diseases. Detailed clinical evaluation can provide reasonable diagnostic accuracy for most patients. A detailed neurological examination is necessary to rule out other diseases. In Alzheimer's disease, the neurological examination is usually normal. Physical examination is normal except for anosmia. Anosmia is also seen in patients with Parkinson's disease and #039 disease, dementia with Lewy bodies, and dementia with or without TBI, but not in patients with VCI or depression. In advanced stages of Alzheimer's disease, patients do not have side symptoms. Later, they become mute, unresponsive to verbal requests, bedridden, and often slip into a permanent vegetative state. A mental status examination should assess concentration, attention, short and long-term memory, language, visual function, practice, and executive function.

EVALUATION

Routine laboratory tests show no specific abnormalities. Complete blood count (CBC), complete metabolic panel (CMP), thyroid-stimulating hormone (TSH) and B12 are usually checked to rule out other causes. CT brain shows cerebral atrophy and the third ventricle is enlarged. This is suggestive, but it is not specific, as these abnormalities also occur in people with other diseases and normal aging-related changes. Analysis of the cerebrospinal fluid (CSF) for low beta-amyloid 42 and elevated tau is useful for preclinical diagnosis. The EEG usually shows generalized slowing without foci. It is diagnostically useful but still nonspecific.

The most reliable method to detect mild cognitive impairment in the early stages of the disease is neuropsychological testing. More recently, volumetric MRI has been used to accurately measure changes in brain volume. In Alzheimer's disease, volumetric MRI shows shrinkage of the medial temporal lobe. However, hippocampal atrophy is also associated with memory loss associated with normal aging, making the use of Volumetric MRI for early detection of Alzheimer's and #039 disease questionable. The role of volumetric MRI in the diagnosis of Alzheimer's disease has not yet been fully established. Functional brain imaging techniques such as PET, fMRI, and SPECT are used to map patterns of dysfunction in smaller brain regions of the medial temporal and parietal lobes. These studies can be useful for early detection and monitoring of clinical courses; However, their role in the diagnosis of Alzheimer's disease has not yet been fully confirmed.

TREATMENT AND MANAGEMENT

There is no cure for Alzheimer's disease. Only sympathy 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

Alzheimer's disease destroys the neurons that make acetylcholine. So over time, you have less than you need. The acetylcholine you do have is gradually broken down as it gets used. Cholinesterase inhibitors slow this process. That makes more of the chemical available to your brain for as long as possible. The FDA has approved three cholinesterase inhibitors for Alzheimer's treatment. Donepezil (Aricept) treats mild, moderate, and severe Alzheimer's disease.

Donepezil can be used in all stages of Alzheimer's disease. Galantamine and rivastigmine are approved for the treatment of MCI and dementia. Donepezil and galantamine are rapid, reversible acetylcholinesterase inhibitors. Rivastigmine is a slow, reversible inhibitor of acetylcholinesterase and butyrylcholinesterase. Donepezil is generally preferred for everyone because it is administered once a day. Galantamine is available as a twice-daily tablet or a once-daily extended-release capsule. It cannot be used to treat end- stage kidney disease or severe liver failure. Rivastigmine is available orally and trans dermally.

Partial N-Methyl D-Aspartate (NMDA) Memantine

Memantine, a partial N-methyl-D-aspartate (NMDA) antagonist, blocks NMDA receptors and slows intracellular calcium accumulation. It is approved by the FDA for the treatment of moderate to severe Alzheimer's disease. Dizziness, body aches, headache and constipation are common side effects. It can be taken with cholinesterase inhibitors.It is also important to treat anxiety, depression, and psychosis, which often occur in the middle or late stages of Alzheimer's disease. Avoid tricyclic antidepressants because of their anticholinergic effects. Antipsychotics are used for acute anxiety only when the patient or caregiver is exhausted. But their limited benefits must be weighed against the small risk of stroke and death.

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

DIFFERTIAL DIAGNOSIS

Differential diagnosis of Alzheimer dementia includes- Pseudodementia, Lewy body dementia, Vascular dementia, and frontotemporal lobar degeneration. Other disorders to consider and rule out when evaluating for Alzheimer's disease include age-associated memory impairment, alcohol or drug abuse, vitamin-B12 deficiency, patients on dialysis, thyroid problems, and polypharmacy.

Lewy Body Dementia (DLB):

About 15% of dementia cases may be due to DLB. DSM-5 includes it in neurocognitive disorders with Lewy bodies. Cortical Lewy bodies are the histological abnormalities seen in these patients. The concentration of bodies of Lewy correlates with the severity of dementia. These bodies are spherical intracytoplasmic inclusions consisting of a dense round eosinophilic core surrounded by loose fibrils. The nucleus contains aggregates of α-synuclein and ubiquitin proteins. Patients with Lewy body dementia have core clinical features (fluctuating thinking, visual hallucinations, one or more Parkinsonian symptoms that begin after cognitive decline), suggestive clinical features (REM sleep behavior disorder and severe antipsychotic sensitivity), and indicative biomarkers. (123-MIBG shows low uptake, SPECT or PET shows reduced dopamine transporter in the basal ganglia, and PSG shows REM sleep without atonia).

Frontotemporal Dementia (FTD):

It accounts for 5 to 10 percent of all cases of dementia. The average age of onset is 53 years and it occurs more often in men than women. Patients with frontotemporal dementia present with personality and behavioral disturbances with or without language impairment that precede insidious dementia. Pick disease is an older term for FTD based on the histological findings of intraneuronal inclusions called "Pick bodies". FTD has two subtypes, the behavioral variant and the linguistic variant. For the behavioral variant, a possible diagnosis requires the patient to have three of the following symptoms: inhibition, apathy, loss of sympathy, stereotyped or

compulsive behavior, hyperorality, and impaired social thinking and executive skills. The language ability of the language variant is weakened.

Dialysis Dementia:

Dialysis dementia is a neurological complication of chronic dialysis. The cause can be vascular (because dialysis patients have a higher risk of stroke) or metabolic disorders or dialysis itself. It was previously thought to be due to the toxicity of aluminum, but today it is rare because alternatives to aluminum- containing substances are used. The exact mechanism is still unclear.

Some atypical presentations of Alzheimer disease include: Posterior cortical atrophy manifests as progressive cortical visual impairment with features such as simultagnosia, object, and space perception deficits, acalculia, alexia, and oculomotor apraxia, with relative sparing of anterograde memory, non-visual language function, behavior, and personality. Neuroimaging shows occipitoparietal or occipitotemporal atrophy. Primary progressive aphasia is characterized by progressive language difficulty with relative sparing of memory and other cognitive functions in early disease. Dysexecutive or frontal variant patients have impairment in executive functions relative to memory loss.

STAGING

Preclinical or Presymptomatic

In this stage, are asymptomatic and have clear laboratory evidence. Identifying biomarkers helps diagnose Alzheimer's disease at this stage. Low amyloid and increased tau proteins in CSF serve as biomarkers but are not specific for Alzheimer's disease.

Mild Cognitive Impairments

Mild cognitive impairment (MCI) is a condition that affects memory and cognitive abilities. People with MCI may experience difficulties with remembering things, paying attention, or solving problems. However, these difficulties are not severe enough to disrupt their daily activities. MCI can be caused by various factors, such as aging, medical conditions, or certain medications. It's important to note that not everyone with MCI will develop dementia, but it does increase the risk. If you or someone you know is experiencing memory or cognitive issues, it's best to seek advice from a healthcare professional who can provide a proper evaluation and guidance.

Dementia

Dementia is a broad term that refers to the impairment of cognitive abilities, including memory, thinking and reasoning, to the point where it affects daily activities. It is more severe than mild cognitive impairment (MCI). Dementia can be caused by a variety of conditions, such as Alzheimer's disease, vascular dementia or Lewy body dementia. Symptoms may include memory loss, confusion, language disturbances, and changes in mood or behavior. If you or someone you know is experiencing these symptoms, it is important to consult a doctor for proper diagnosis and guidance. Dementia is not a specific disease but a syndrome. It involves a decline in cognitive function beyond what might be expected from normal aging.

PROGNOSIS

Progression: Alzheimer's disease tends to worsen over time, typically progressing through stages from mild cognitive impairment to severe dementia.

Duration: The duration of the disease varies. Some individuals may live for several years with Alzheimer's, while others may experience a more rapid decline.

Life Expectancy: On average, individuals with Alzheimer's disease live about 4 to 8 years after diagnosis, but this can vary based on factors like age, overall health, and the presence of other medical conditions.

ENHANCING HEALTHCARE TEAM OUTCOMES:

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by behavioral and cognitive decline that ultimately interferes with daily functional life. The disease is not curable and the rate of progression varies. In addition, early diagnosis of Alzheimer's disease is difficult, and there are no specific laboratory or imaging tests to confirm the diagnosis. The drugs available to treat this disease only work in mild cases, but they also have many side effects that are not well tolerated. Alzheimer's disease is a systemic disease and devastates the family. These individuals often wander, fall, have serious behavioral problems and memory loss. The following health care workers have a critical role in ensuring that the patient with Alzheimer disease remains safe and lead a decent quality of life. Physical therapy for exercise. There is now ample evidence that exercise can help reduce the progression of the disease. Nurses to educate the patient and family on medications, lifestyle changes, and performing daily living activities. To educate the partner on self-reporting on the worsening of symptoms. Pharmacist to ensure that polypharmacy does not occur and that the patient is not developing adverse effects. Clinicians to monitor patient progress and enhance the quality of life. Caregivers to provide support.

OUTCOMES

Alzheimer's disease initially involves only memory loss, but over time a person can develop severe cognitive .

and behavioral symptoms such as depression, anxiety, anger, irritability, insomnia and paranoia. As the disease worsens, most of them need help in everyday life. Eventually, even walking becomes difficult, and many may not eat or have difficulty swallowing, leading to aspiration pneumonia.

CONCLUSION

Alzheimer's disease is one of the most common causes of dementia. It is a progressive brain disease that affects memory, thinking and behavior. As the disease progresses, people may have difficulty performing daily tasks and experience changes in personality and behavior. Although there is no cure for Alzheimer's disease, there are treatments to help manage symptoms and improve quality of life. It is important to consult a doctor to make a correct diagnosis and explore available treatment options.

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